During the study period, the following assessments were to be made: pain intensity at hours 0-, 0.5-, 1-, 2-, 3-, 4-, 6-, 8-, 12-, 16-, 20-, and 24; number of LED flashes; vital signs; oxygen saturation. At each scheduled assessment, patients were asked to perform activities such as coughing, deep breathing as appropriate. As per the JCAHO guidelines, patients were also asked to determine whether the required activities for early recovery could be performed comfortably. Patients were not to receive analgesic medications, consume alcohol or taken a shower during the study period.

At the termination of the study period, patients and investigators were to give their global assessments of the therapy.

Patients were considered to have completed the study if they had done any of the following:

- Completed the 24 hour treatment period
- Were discharged from the hospital
- No longer required parenteral opioids

Patients could be withdrawn from the study for any of the following:

- Inadequate pain control
- Two E-TRANS systems in a given patient were suspected of having technical failures (original and a replacement)
- Patient withdrew consent
- Adverse Event/Serious Adverse Event
- Two episodes of clinically relevant respiratory depression, defined as simultaneous bradypnea and excessive sedation.
- No further requirement for opioid analgesia
- Hospital discharge

The first subject was treated on this protocol on November 13 2001 and the last treatment was completed on March 13 2002. The first amendment to the protocol was made on September 6 2001, prior to enrolling any patients in this study. The second amendment was made after the study had started.

- Amendment 2, dated March 12 2002, eliminated the planned interim data analyses. Enrollment was faster than had been expected so the full cohort of 474 patients accrued within weeks of the planned interim analysis of 250 patients.

Outcome measures:

Primary efficacy measurement

- Number of patients in each treatment group who dropped out of the study more than three hours after initiation of therapy due to inadequate pain control

Secondary efficacy measurements

- Number of dropouts for any reason
- Pain intensity
- Patient global assessment

- Investigator global assessment
- Assessment of the adherence of the E-TRANS system

Study results:

Patient demographics:
Of the 630 patients who were screened, 484 were eligible for trial entry and randomization: 244 received E-TRANS fentanyl and 240 received E-TRANS placebo. The evaluable population, defined as patients who remained in the study for three hours or more, included 439 patients, 235 of whom received E-TRANS fentanyl. The evaluable patients were predominantly Caucasian (n=372) with the rest described as Black (n=39), Hispanic (n=19), Asian (n=6) or other (3). The majority were female (n=308, 70.2%). Most of the evaluable patients (n=206) had lower abdominal surgery (bowel, genitourinary or gynecological) or orthopedic surgery (n=206). Thirteen had thoracic/chest surgeries. Six had upper abdominal surgery and eight had other surgeries.

Table 17:
Demographics summary table of the 439 evaluable patients[a]

	Fentanyl (n=235)	**Placebo (n=204)**	**Total (n=439)**
Gender			
Female	165 (70.2%)	143 (70.1%)	308 (70.2%)
Male	70 (29.8%)	61 (29.9%)	131 (29.8%)
Age			
Median	54	54	54
Range	22-86	18-90	18-90
Race			
Caucasian	198 (84%)	174 (85%)	372 (85%)
Black	23 (10%)	16 (8%)	39(9%)
Asian	5 (2%)	1	6 (1%)
Hispanic	7 (3%)	12 (6%)	19 (4%)
Other	2 (1%)	1 (1%)	3 (1%)
Surgery			
Lower abdominal	113 (48%)	93 (46%)	206 (47%)
Upper abdominal	2 (1 %)	4 (2%)	6 (1.4%)
Orthopedic	110 (47%)	96 (47%)	206 (47%)
Thoracic/Chest	6 (3%)	7 (3%)	13 (3%)
Other	4 (2%)	4 (2%)	8 (2%)
ASA status			
I	23 (10%)	26 (13%)	49 (11%)
II	170 (72%)	121 (59%)	291 (66%)
III	42(18%)	57 (28%)	99 (23%)

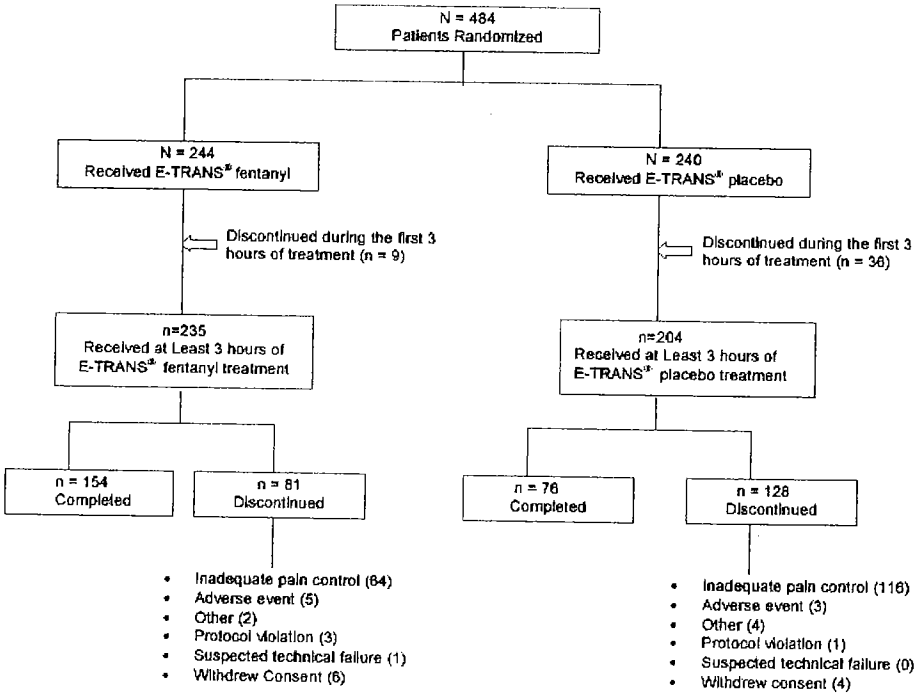
[a]This is a combination of Tables F.G and H from the study report

Forty-five patients discontinued within the first 3 hours of the study. Nine patients in the E-TRANS fentanyl group withdrew: 6 for inadequate analgesia, 1 due to an adverse event (901); 1 due to a protocol violation (1408); 1 due to withdrawn consent. The remaining patients were receiving E-TRANS placebo. The majority of these patients withdrew due to inadequate analgesia (n=28), with the rest withdrawing due to suspected technical failure (5), withdrawn consent (2) or other reasons (1).

Eighty-one (34%) of the patients in the E-TRANS fentanyl group discontinued after 3 hours but prior to 24 hours of system use: 64 due to inadequate pain control after the first three hours; 5 due to adverse events (1452,1760,1819,1836,2002); 3 due to protocol violations (1426,2012,2137); 1 due to suspected technical failure (1820); 6 withdrew consent (403,714,1228,1702,1724,1824,2071); 2 withdrew for "other reasons (1739,1759)."

One hundred twenty-eight (63%) of the patients in the placebo group discontinued after 3 hours but prior to 24 hours of system use: 116 due to inadequate pain control after the first three hours; 3 due to adverse events (207, 405, 1722); 1 due to protocol violation (2139);4 withdrew consent (1111,1602, 1734,2041); 4 withdrew for "other reasons" (1701,1752, 1848, 2032).

Table 18:
Patient disposition



Source: Tables 11.2.2-1 and 11.3.2-1.

Protocol violations:
Table 19:

Protocol Deviations (Treated Patients)

	E-TRANS(fentanyl) 40 µg (n=244)	Placebo (n=240)	Total (n=484)
Inclusion/Exclusion Criteria[a]	6 (4.6%)	6 (5.2%)	12 (4.9%)
Disallowed medications given pre-enrollment (intra-op/post-op)	8 (6.1%)	8 (6.9%)	16 (6.5%)
Opioids other than fentanyl rescue given hrs 0-3	8 (6.1%)	1 (0.9%)	9 (3.6%)
Opioids given >= hr3	8 (6.1%)	7 (6.0%)	15 (6.1%)
Disallowed analgesics(other than opioids)	12 (9.2%)	5 (4.3%)	17 (6.9%)
Procedural[b]	87 (66.4%)	89 (76.7%)	176 (71.3%)
Other	2 (1.5%)	0	2 (0.8%)

Note: A patient may be tabulated in more than one protocol deviation type
[a] (Other than prohibited medications or procedures not done)
[b] (Assessments/evaluations performed out of order, out of window, or not done)

(Reviewer's note: The table above uses the number of patients with reported protocol violations in each category as the denominator not the total number of treated patients per category: 130 patients in the active group reported protocol violations; 115 patients in the placebo group reported protocol violations.)

The two protocol violations recorded as "other" both led to study discontinuation. The family of patient 1739 was administering the on-demand dosing contrary to the instruction that only the patient was to use the E-TRANS system. Patient 2137 wore the system into a magnetic resonance imaging device, whose electromagnetic field was strong enough to disable the system.

ALZA did a post hoc analysis of the efficacy data from the evaluable study population excluding those evaluable (13 E-TRANS fentanyl and 9 placebo) patients who received prohibited medications during the trial as well as a post hoc analysis re-categorizing those patients as early discontinuations due to inadequate analgesia. In both cases, they reported statistically significant differences between the treatment arms when dropouts due to inadequate analgesia, dropouts for any reason and global assessments were reviewed.

Safety
Analysis of safety results will be deferred to the Section VII of this review, Integrated Review of Safety.

Efficacy results:
Primary efficacy measurement

- Number of patients in each treatment group who dropped out of the study more than three hours after initiation of therapy due to inadequate pain control. The protocol specified that a patient was to be considered evaluable if she/he received at least 3 hours of treatment with E-TRANS fentanyl or E-TRANS placebo.

When the results from the evaluable population was analyzed, the difference between the percentage of dropouts in the placebo group (57%, n=116/204) and the percentage of dropouts in the E-TRANS fentanyl group (27%, n=64/235) was statistically significant, p-value<0.0001.

When the results from the entire treated population was analyzed, the difference between the percentage of dropouts in the placebo group (60%, n=144/240) and the percentage of dropouts in the E-TRANS fentanyl group (29%, n=70/244) remained statistically significant, p-value<0.0001.

Logistic regression analysis demonstrated that evaluable patients who required rescue during the first three hours of the study period were 2.775 times more likely to drop out due to inadequate analgesia. The results were similar when the model used all treated patients as the population of interest.

Table 20:

Withdrawals due to Inadequate Pain Relief

	E-TRANS® (fentanyl) 40 µg	Placebo	p-value
Evaluable Patients (N)	235	204	
Withdrawals due to inadequate pain relief	64 (27.2%)	118 (58.9%)	<0.0001
Duration of treatment[a] (h)			
Mean (SEM)	7.6 (0.74)	7.6 (0.48)	
Median (range)	4.6 (3.0-22.5)	5.4 (3.0-22.1)	
Treated Patients (N)	244	240	
Withdrawals due to inadequate pain relief	70 (28.7%)	144 (60.0%)	<0.0001
Duration of treatment[a] (h)			
Mean (SEM)	7.3 (0.70)	6.5 (0.43)	
Median (range)	4.3 (1.1-22.5)	4.2 (1.0-22.1)	

[a] For patients who withdrew due to inadequate analgesia

Source: Tables 11.2.3-1 and 11.3.3-1

Secondary efficacy measurements

- Overall dropout rate regardless of termination reason during the 24 hour treatment period

When the results from the evaluable population were analyzed, the difference between the percentage of dropouts for any reason in the placebo group (63%, n=128) and the percentage of dropouts in the E-TRANS fentanyl group (34%, n=81) was statistically significant, p-value<0.0001. When dropouts for any reason in the entire treated population were reviewed, the difference was still statistically significant, p-value<0.0001.

Table 21:

Withdrawals for Any Reason

	E-TRANS® (fentanyl) 40 µg	Placebo	p-value
Evaluable Patients (N)	235	204	
Withdrawals for any reason	81 (34.5%)	128 (62.7%)	<0.0001
Duration of treatment[a] (h)			
Mean (SEM)	8.7 (0.71)	7.6 (0.47)	
Median (range)	5.6 (3.0-22.5)	5.3 (3.0-23.3)	
Treated Patients (N)	244	240	
Withdrawals for any reason	90 (36.9%)	164 (68.3%)	<0.0001
Duration of treatment[a] (h)			
Mean (SEM)	8.0 (0.68)	6.4 (0.41)	
Median (range)	4.5 (0.1-22.5)	4.0 (0.2-23.3)	

[a] For patients who withdrew for any reason

Source: Tables 11.2.3-1 and 11.3.3-1

- Mean pain intensity over the 24-hour treatment period (0-10 VAS)

  Five minutes prior to each pain assessment, patients were told to breath deeply/cough as appropriate in order to achieve a clinically meaningful pain assessment. Pain assessments were done at Hour 0, 1-,2-,3-,4-, 6-, 8-, and every 4 hours through the rest of the study treatment.

  If a patient withdrew prior to a scheduled pain intensity assessment, a measurement was made at the time of withdrawal which would be carried forward to the scheduled pain intensity assessment. The VAS was considered missing when the patient was asleep.

  The mean pain intensity over the 24-hour treatment period was to be computed for each patient. The mean pain intensity was defined as the mean of the available VAS measurements after Hour 0 and during the 24 hour treatment period for a given patient.

  The mean pain intensity score was 3.4 (+/- 0.16) in the 235 evaluable patients receiving E-TRANS fentanyl, an increase of 0.4 from baseline. The mean pain intensity score was 5.3 (+/- 0.18) in the 204 evaluable patients receiving placebo, an increase of 2.2 from baseline. The difference was statistically significant with a p-value of <0.0001.

  When all of the patients who been randomized (all treated patients) were evaluated the mean pain intensity score was 3.5 (+/- 0.16) in the 244 patients receiving E-TRANS fentanyl. The mean pain intensity score was 5.4 (+/- 0.17) in the 240 evaluable patients receiving placebo. The difference was statistically significant with a p-value of <0.0001.

- Investigator global assessment at termination (4-point categorical scale)

  If a patient was withdrawn from the study prior to 24 hours, the global assessment used at the time of the withdrawal would be used for the 24-hour time point, a last observation carried forward analysis. Success was defined as a response of excellent (4) or good (3). Failure was defined as a response of fair (2) or poor (1). In the p-value calculation, missing values were assumed to be 1 (poor).

  A higher proportion of evaluable patients in the fentanyl group (75%, n= 176/235) rated treatment as a success than in the placebo group (52%, n=107/204), p-value <0.0001. The results for the all treated patient group were similar.

  Table 22:

Investigator Global Assessment Dichotomous Categories

	E-TRANS® (fentanyl) 40 µg	Placebo	p-value
Evaluable Patients			
N	235	204	<0.0001
Success	176 (74.9%)	107 (52.5%)	
Failure	58 (24.7%)	97 (47.1%)	
Treated Patients			
N	244	240	<0.0001
Success	176 (72.1%)	112 (46.7%)	
Failure	66 (27.0%)	123 (51.3%)	

Note: If the investigator global assessment was missing, it was assumed to be a "Failure" for the p-value calculation.

Source: Tables 11.2.3-10 and 11.3.3-10

- Patient global assessment at termination (4-point categorical scale)

  If a patient was withdrawn from the study prior to 24 hours, the global assessment used at the time of the withdrawal would be used for the 24-hour time point, a last observation carried forward analysis. Success was defined as a response of excellent (4) or good (3). Failure was defined as a response of fair (2) or poor (1). In the p-value calculation, missing values were assumed to be 1 (poor).

  A higher proportion of evaluable patients in the fentanyl group (76%, n= 179/235) rated treatment as a success than in the placebo group (52%, n=106/204), p-value <0.0001. The results for the all treated patient group were similar.

  Table 23:

Patient Global Assessment Dichotomous Categories

	E-TRANS® (fentanyl) 40 µg	Placebo	p-value
Evaluable Patients			
N	235	204	<0.0001
Success	179 (76.2%)	106 (52.0%)	
Failure	56 (23.8%)	97 (47.5%)	
Treated Patients			
N	244	240	<0.0001
Success	179 (73.4%)	110 (45.8%)	
Failure	63 (25.8%)	125 (52.1%)	

Note: If the patient global assessment was missing, it was assumed to be a "Failure" for the p-value calculation.

Source: Tables 11.2.3-8 and 11.3.3-8

- Pain management goal

  Patients were asked, prior to surgery, to select a pain rating that would not interfere with their recovery. The majority of evaluable patients (90%) designated a score of less than 4.

  There was a significant difference (p-value <0.0001) in the proportion of evaluable patients who were able to achieve their stated goal, 64.7% of the E-TRANS fentanyl patients and 37.3% of the placebo patients. Of the dropouts, 62 of the 64 evaluable E-TRANS fentanyl patients and 110 of the 116 evaluable placebo patients had not met their goals at the time of discontinuation.

- Patients who required rescue medication during the first 3 hours after E-TRANS application

  While in the evaluable population, a slightly higher proportion of the placebo group used rescue (52% vs. 45%) the difference between the treatment arms was not significant. When the results from all treated patients were analyzed, the difference between the placebo and active treatment arms reached statistical significance (58% vs. 46%, p-value 0.0082).

- Assessment of the adherence of the E-TRANS system

  Approximately ninety percent of the evaluable patients in each treatment group had the system adhered to at least 90% of the area with no unattached edges (89% of the active group and 92% of the placebo group).

- Suspected technical failures

  There were 17 reports of technical failures with E-TRANS fentanyl systems. ALZA' analysis showed '

  There were 42 reports of technical failures with E-TRANS placebo systems·

Sponsor's Post hoc analyses

ALZA did a post hoc analysis excluding the 22 patients (13 active/9 placebo) who received an opioid, NSAID or COX-2 inhibitor after Hour 3. Another post hoc analysis

was done with these patients re-categorized as having been dropouts due to inadequate analgesia. The efficacy results for dropouts due to inadequate analgesia and dropouts for any reason remained statistically significant between the groups (p-value <0.0001).

Reviewer's conclusions from the efficacy results in study C-2001-011

The protocol defined the primary efficacy measurement as discontinuations due to inadequate pain control more than three hours after application of study therapy due to inadequate pain control and specified use of an evaluable population for the primary efficacy analyses instead of an intent-to-treat population. When the results from the evaluable population was analyzed, the difference between the percentage of dropouts in the placebo group (57%, n=116/204) and the percentage of dropouts in the E-TRANS fentanyl group (27%, n=64/235) was statistically significant. The results remained statistically significant when the entire treated population was analyzed.

If one looks at the percentage of dropouts in each treatment group who discontinued before 24 hours due to inadequate analgesia-there is a clear difference. Of the 81 patients in the E-TRANS fentanyl group who discontinued after 3 hours but prior to 24 hours of system use, 64 (79%) discontinued due to inadequate pain control. Of the 128 patients in the E-TRANS placebo group who discontinued prior to 24 hours of system use, 116 (91%) discontinued due to inadequate pain control. This is consistent with the conclusion that the E-TRANS fentanyl system was providing some benefit over placebo in an appropriately chosen patient population.

This trial showed benefit of the active drug as compared to placebo in patients who had been appropriately titrated to comfort before beginning use of E-TRANS fentanyl, i.e. those with a PACU score less than 5/10. The trial was able to demonstrate efficacy of the E-TRANS fentanyl system in a patient population appropriately screened for potential use of patient-controlled analgesia.

C-2000-007

Title:

The safety and efficacy of electrotransport (E-TRANS) fentanyl compared to IV PCA morphine for the treatment of postoperative pain.

Objective:

- Compare the safety and efficacy of the E-TRANS fentanyl system with intravenous patient-controlled analgesia for the management of post-operative pain

Population:

Six hundred thirty six adult patients were randomized to treatment with 316 receiving active drug and 320 receiving IV PCA morphine.

Inclusion criteria:

- Adults of either gender
- Post operative ASA I, II, III status, as defined in Appendix A
- Females of child-bearing age were to have negative pregnancy tests, though an exception was made for women who were having elective cesarean sections or hysterectomies
- Admission to the post-anesthesia care unit after general or regional anesthesia for major abdominal, orthopedic or thoracic surgery
- Expectation of moderate to severe pain requiring opioids for at least 24 hours post-operatively
- Patients who had been in the PACU for at least 30 minutes and who were comfortable or had been titrated to comfort with intravenous opioids
- Awake patients who were breathing 8-24 breaths/minute spontaneously with an oxygen saturation of 90% or greater (with or without supplemental oxygen)

Exclusion criteria:

- Patients expected to have post-operative analgesia supplied by a continuous regional technique or who had received a long-lasting intra-operative regional analgesic
- Patients who received intra-operative or post-operative administration of opioids other than morphine, fentanyl, sufentanil or alfentanil. Patients were allowed to receive up to 50 mg of meperidine as treatment for shivering within 30 minutes of arrival in the PACU.
- History of allergy or hypersensitivity to fentanyl , skin adhesives and/or cetylpyridinium chloride
- Patients expected to need intensive care or to require additional surgery within 36 hours
- Known or suspected opioid tolerance
- History of opioid dependence within 3 months of starting the study
- Illicit drug use, prescription drug abuse or alcohol abuse within 30 days before the start of the study
- Active systemic skin disease

- Increased intracranial pressure
- Women who were pregnant (unless scheduled for an elective cesarean section), breastfeeding or planning to breast feed within 30 days of the last dose of study drug
- Patients whose post-operative care would normally require treatment other than parenteral opioids alone
- Patients who had chest tubes in place post-operatively
- Patients who are intubated at the time of final screening assessments
- Patients with any coexisting medical condition that is likely to interfere with study procedures

Study design:
A multi-center, randomized, open-label, active-controlled, parallel-group study conducted in the United States of America.

Study duration:
Up to 72 hours per participant

Study procedure:
After surgery patients were to be taken to the PACU, where they were to receive titration with IV opioids if needed. After a patient had been awake, alert and comfortable in the PACU for at least 30 minutes, he/she was to be assessed for pain and oxygen saturation. Vital signs were to be obtained at this time.

If the rest of the entry criteria were met, patients were eligible for study participation and were to be randomized to receive either E-TRANS fentanyl or IV morphine PCA for the next 24 hours. If patients continued to require parenteral opioids after the first 24 hours of treatment, they could receive an additional 48 hours of treatment for a total of 3 24-hour treatment periods.

Baseline assessments of pain intensity, vital signs and oxygen saturation were to be done, Hour 0. The assigned treatment was to be started immediately after the Hour 0 assessment.

Patients were to be observed in the recovery room for one hour after initiation of study treatment before going into a regular hospital room for the remainder of the study period. Intravenous fentanyl or morphine, depending on the randomization assignment, was to be allowed as rescue medication during the first three hours after study system application.

During the study period, the following assessments were to be made: pain intensity at hours 0-, 0.5-, 1-, 2-, 3-, 4-, 6-, 8-, 12-, 16-, 20-, and 24; number of LED flashes; vital signs; oxygen saturation.

At each 24-hour assessment period, patients and investigators were to give their global assessments of the therapy. If the patient was withdrawn from the study prior to a 24 hour

time point, pain intensity assessment and global impressions were to be gathered at the time of withdrawal.

Erythema was to be evaluated 24 hours after removal of the E-TRANS fentanyl system. The E-TRANS system was to be removed and/or replaced for the remainder of the 24 hour period if the system no longer responded to a demand for a dose or if the system fell off. The new system was to be applied to a different site and removed at the same time that the original one was scheduled to be removed.

If the PCA morphine infusion line were to infiltrate, it was to be replaced at a different site.

Patients were to have two blood samples drawn to confirm delivery of fentanyl or morphine. Patients who remained on study for more than 3 hours were to have one sample drawn prior to administration of an on-demand dose and one drawn 15 minutes after dose initiation.

Serum samples were to be collected to determine opiate concentration if a SAE occurred that was judged possibly or probably related to study treatment.

The first subject treated on this protocol began on September 18 2000 and the last treatment was completed on March 11 2001.

The only amendment to the protocol was made on August 2 2000, prior to enrolling any patients in this study.

Outcome measures:
Primary efficacy measurement
- Patient global assessment at 24 hours

Secondary efficacy measurements
- Pain intensity (VAS 0-100)
- Patient global assessments at 48 and 72 hours
- Investigator global assessments at 24, 48 and 72 hours
- Number of patients with inadequate pain control
- Assessment of the adherence of the E-TRANS system

Study results:
Description of patients:
Of the 726 patients who were screened, 636 were eligible for trial entry and randomization: 316 received E-TRANS fentanyl and 320 received IV PCA morphine.

The evaluable population, i.e. those who remained on study for more than 3 hours, included 626 patients. 310 of whom received E-TRANS fentanyl. The evaluable patients were predominantly Caucasian (n=458) with the rest described as black (n=117), Hispanic (n=38), Asian (n=6) or other (7). The majority were female (n=462, 74%).

Table 24:
Demographics summary table of the 626 evaluable patients[a]

	E-TRANS Fentanyl (n=310)	IV Morphine (n=316)	Total (n=626)
Gender			
Female	226 (73%)	236 (75%)	462 (74%)
Male	84 (27%)	80 (25%)	164 (26%)
Age			
Median	49	48	49
Range	18-90	18-86	18-90
Race			
Caucasian	227 (73%)	231 (73%)	458 (73%)
Black	55 (17%)	62 (20%)	117(19%)
Asian	3 (1%)	3 (1%)	6 (1%)
Hispanic	22 (7%)	16 (5%)	38 (6%)
Other	3 (1%)	4 (1%)	7 (1%)
Surgery[b]			
Group I: Lower abdominal, orthopedic,thoracic	129 (41%)	127 (40%)	256 (41%)
Group II: Upper abdominal,other	183(59 %)	190 (60%)	373 (59%)
ASA status			
I	56 (18%)	52 (17%)	108 (17%)
II	208 (67%)	215 (68%)	423 (68%)
III	46 (15%)	49 (16%)	95 (15%)

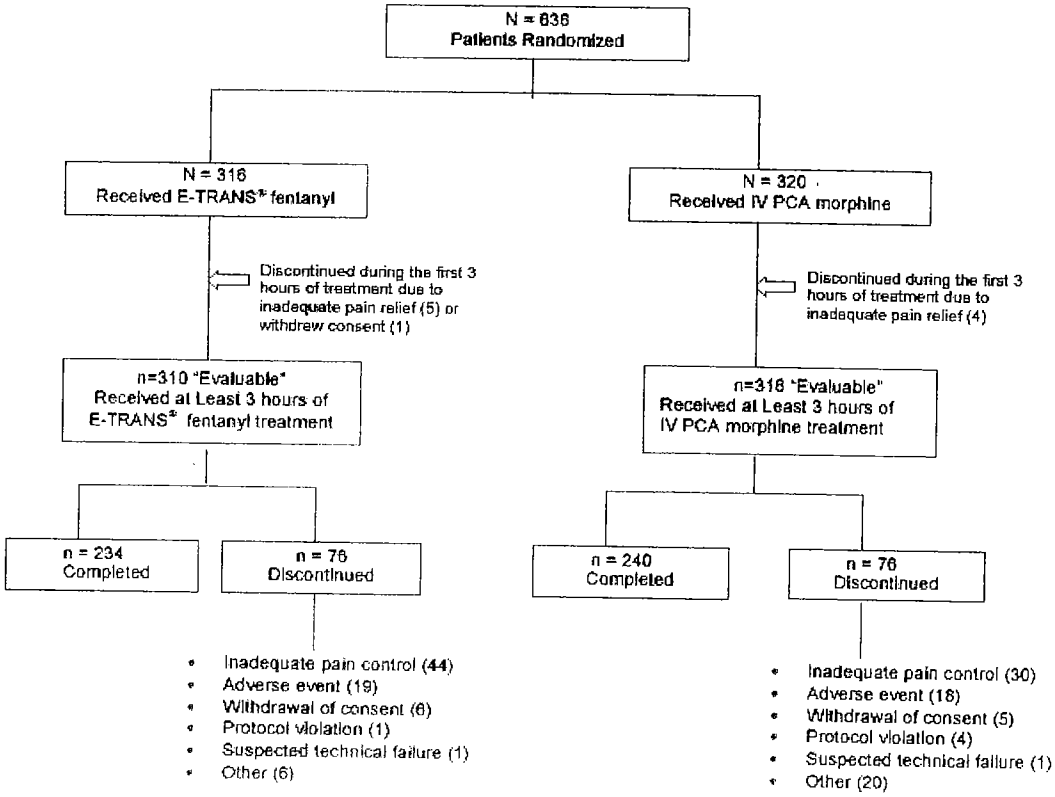
[a]This is a combination of Tables H, I and K from the study report
[b]This study divided the patients into "stratification groups" by type of surgery, however, review of the surgery subtypes revealed that the proportion of specific surgery types within each stratification group was similar in the two groups.

Ten patients discontinued within the first 3 hours of the study. Six patients in the E-TRANS fentanyl group withdrew: 5 for inadequate analgesia; 1 due to withdrawn consent. The remaining four patients were receiving IV morphine. All of these patients withdrew due to inadequate analgesia.

Seventy-six of the 310 evaluable patients in the E-TRANS fentanyl group discontinued after 3 hours but prior to 72 hours of system use: 47 (62%) due to inadequate pain control after the first three hours; 19 (25%) due to adverse events; 1 (1%) due to protocol violations; 1 (1%) due to suspected technical failure; 6 (8%) withdrew consent; 3 (4%) withdrew for "other reasons." One patient had two reasons for discontinuation, both adverse event and inadequate analgesia (129)

Seventy-six of the 316 evaluable patients in the IV morphine group discontinued after 3 hours but prior to 72 hours of system use: 42 (55%) due to inadequate pain control after the first three hours; 18 (24%) due to adverse events; 4 (5 %) due to protocol violation; 1 (1%) due to suspected technical failure; 5 (7%) withdrew consent; 8 (11%) withdrew for "other reasons." Three of these patients had more than one reason for discontinuation: protocol violation and no further need for opioid in patient 129; inadequate analgesia and other in patient 505; adverse event and protocol violation in patient 2903.

Table 25:
Patient disposition



Note: Four patients (1 E-TRANS®, 3 IV PCA) had two reasons for discontinuation: E-TRANS® patient 129 termination reasons are adverse event and inadequate analgesia; IV PCA patient 131 termination reasons are no further need for parenteral opioid analgesia and protocol violation; IV PCA patient 505 termination reasons are inadequate analgesia and other; and IV PCA patient 2903 termination reasons are adverse event and protocol violation. For IV PCA patient 131, the termination reason of no further need for parenteral opioid analgesia was counted in the completed column.

Protocol violations

Three patients were enrolled who did not meet the screening criteria. One patient who had used an illicit drug of abuse within 14 days of surgery was randomized to E-TRANS fentanyl (1424). One patient randomized to IV morphine, did not have a pregnancy test

preformed prior to study entry. A third patient, also randomized to IV morphine, had received remifentanyl intraoperatively. All three were granted waivers for study participation. These three patients did not have protocol violations that would affect the assessment of efficacy and therefore these subjects were included in the analysis.

The majority of the reported protocol violations during the study involved assessments that were either missed or not done at the time specified in the protocol. Forty-eight patients took analgesic medication in addition to the study drug, as shown in the table below. None of these patients were excluded from the efficacy analyses.

Table 26:

TABLE G
Summary of Protocol Deviations Affecting Study Drug Administration

	E-TRANS® (fentanyl) 40 µg (N=316)	IV PCA Morphine (N=320)
Other analgesic medications taken	24 (7.6%)	24 (7.5%)
Incorrect rescue medication given	17 (5.4%)	1 (0.3%)
Morphine dose limited to 6 mg per hour	NA	10 (3.1%)
Morphine dose >10 mg per hour	NA	5 (1.6%)
Morphine bolus dose >1 mg	NA	3 (0.9%)
No doses of morphine recorded	NA	2 (0.6%)
Multiple doses of morphine not recorded	NA	9 (2.8%)
Morphine doses administered by staff	NA	1 (0.3%)
No CRRD blood sample taken	NA	1 (0.3%)

Blood samples were not taken for two patients who had treatment related SAEs (133-confusion, 2903-respiratory depression) because the events were not categorized as serious until after the study had ended.

Outcome measures:
Although ALZA submitted this study as supportive evidence of efficacy for the E-TRANS system, the lack of control for bias inherent in open-label studies precludes the use of this study in support of efficacy.

While E-TRANS showed similar results to IV PCA morphine, this study was not designed as a formal test of equivalence or non-inferiority. The results of this study may be summarized by stating that the E-TRANS system did not significantly separate from IV morphine in terms of patient or investigator assessments at 24-, 48- or 72- hours. A higher proportion of evaluable patients in the IV PCA morphine group (78%, n= 246/316) rated treatment as a success than in the placebo group (75%, n=232/310) but the difference was not statistically significant, p-value <0.3756 (CI –9.7%, 3.7%). The results for the all-treated-patient groups were similar.

D. Efficacy Conclusions

Clinical efficacy

These studies have demonstrated efficacy of the E-TRANS fentanyl system in comparison to placebo in patients who are at least three hours post surgery and have been successfully titrated to comfort with parenteral opioids, i.e. those with PACU scores of 5/10 or less at the time that PCA is initiated. If the total IV opioid requirement for titration to comfort approaches the equivalent of 40 mg morphine sulfate or 400 mcg fentanyl, the patient should be reassessed to determine suitability for PCA opioid as a sole analgesic agent.

The E-TRANS fentanyl system has not demonstrated clear efficacy during the first three postoperative hours since the use of rescue medication was similar in the active and the placebo arms. This device appears to have what is best described as a priming phase, i.e. the first 18-20 doses delivered are under the nominal 40 mcg dose, which would explain the study finding that the use of rescue analgesics was comparable in the two groups during the first 3 hours. It should be noted that after about the 40th dose, the device delivers, *in vivo*, about 44 mcg per dose, a 10% increase over the nominal dose. While the studies show that the effective analgesic dose for iontophoretic delivery of fentanyl lies somewhere between 25 and 40 mcg, it is not clear at what dose analgesia may reliably begin to be noted. Indeed this is probably a matter of individual variation.

Placebo-controlled studies C-95-016 and C-2000-011 demonstrated efficacy of the E-TRANS fentanyl system in patients who are at least three hours post surgery and have been successfully titrated to comfort with parenteral opioids. The predefined primary efficacy measurement was the number of discontinuations due to inadequate pain control after the first three hours of the postoperative period. This difference, which was calculated using the respective evaluable populations as the denominators, is clinically and statistically significant. The predefined secondary efficacy measurements trended towards agreement with the primary efficacy measurement. While the results of subgroup analysis of the adequacy of pain relief by gender and age greater than 65 were not reliable in Study C-96-016 due to the inadequate sample size in the placebo group, E-TRANS was found to demonstrate a positive effect compared to placebo during subgroup analysis done across gender, center and age for Study C-2001-011.

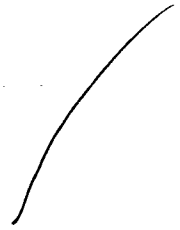
Placebo-controlled study C-2000-008 also demonstrated efficacy of the E-TRANS fentanyl system though with borderline results. In the planned analysis of all treated patients, the difference in dropout rate was not statistically significant with a p-value of 0.070: 48/154 dropped out in the fentanyl group; 23/51 dropped out in the placebo group. Posthoc analysis of all treated patients with a initial VAS score of less than 75 found a statistically significant treatment group difference, p-value of 0.014. A subgroup analysis revealed that the treatment difference in favor of E-TRANS fentanyl was inconsistent across center, gender and age group.

The results from active-controlled study C-2000-007 were also borderline. The success rate for E-TRANS fentanyl was 74.7% as compared to the success rate of 78.8% seen with IV PCA morphine. The 95% confidence interval for this 4.1 % difference was from −10.6% to 2.5%, which is only slightly above the pre-specified equivalence margin of 10%.

Device efficacy

ALZA reported that 8% (72/854) of the E-TRANS systems used in the placebo-controlled trials submitted in support of efficacy had suspected technical failures: 23 of 297 active systems (4.6%); 49 of 357 (14%) placebo systems. In addition, 20 systems (2%) required tape to remain adhered to the patient. ALZA reported that 4% (22/590) of the E-TRANS systems used in the active-controlled trial submitted in support of efficacy had suspected technical failures. Five percent of the IV PCA pumps were suspected of having technical failures.

The types of E-TRANS malfunctions described in the study reports were as follows:



ALZA reports that modifications in the [redacted] as well as modifications to the [redacted] were made in response to the more commonly reported malfunctions.

The adhesion issues were not amenable to modification in the adhesive since alterations in adhesion characteristics can be partially related to aspects of individual patient skin.

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Table 27:

TABLE 3.2.P.9.4.4-A
Number of Suspected Technical Failures Occurring During Clinical Use

Clinical Protocol Number	Dosage (µg)	System Code / Control Number	Systems Used	Suspected Failures	
				Number	Percent
C-94-067	25	0009551 / 0012151	87	5	5.8
C-95-016	40	0003997 / 841396	77	0	0.0
	0	0004597 / 869496	25	3	2.9
C-2000-005	25	0009551 / 0012151	120	3	2.5
		0011808 / 0109005	68	3	4.4
	40	0009747 / 0012149	50	2	4.0
		0011807 / 0109004	3	0	0.0
		0012096 / 0115403	10	2	20.0
C-2000-006	25	0009551 / 0012151	163	9	5.5
C-2000-007	40	0009747 / 0012149	590	22[a]	3.9
C-2000-008	40	0009747 / 0012149	164	6	3.7
	0	0009749 / 0012152	55	4	7.3
C-2000-009	25	0009551 / 0012151	755	51	6.8
C-2001-009	40	0011807 / 0109004	87	5	5.8
C-2001-011	40	0012096 / 0116435	259	17[b]	6.6
	0	0012095 / 0115536	277	42[a]	15.2
C-2002-027	40	0012096 / 0116435	166	8	4.8
TOTAL			2956	183	6.2

[a] Value excludes 1 system not used on a patient, but returned to ALZA.
[b] Value excludes 3 systems not used on a patient, but returned to ALZA.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

The adverse events profile was consistent with that seen with other fentanyl transdermal products. The major difference between this product and the currently marketed fentanyl transdermal products is that E-TRANS is indicated for acute use, including use in postoperative patients. The currently marketed transdermal products are specifically contraindicated in the postoperative period.

No study site reported a patient dying while an E-TRANS system was in place. Five patients died after completing or withdrawing from the study. Three of these patients had deaths attributed to pulmonary embolism. The other two died of sepsis.

The majority of the serious adverse events reported were surgical complications such as wound infection or separation. There were episodes of myocardial infarction in patients who had cardiovascular abnormalities such as atherosclerotic coronary disease. These episodes were probably not related to use of study drug.

There were multiple reports of ileus, which was noted to occur at a higher incidence in patients receiving E-TRANS 40 mcg than in patients receiving placebo. Some of the reports of ileus occurred in conjunction with surgeries that would have involved bowel manipulation. In the latter instances it is unclear whether the decrease in bowel motility was in response to surgical manipulation of the gut or to the use of study drug. Fentanyl, as an opiate is known to decrease bowel motility. The combination of opiate use and post-surgical immotility may have contributed to the duration and severity of ileus in some study participants.

A total of eight embolic events were reported in users of the E-TRANS system: seven patients had a pulmonary embolism; one had an embolic stroke. It is difficult to fully evaluate the significance of this finding since we do not know the background rate of post-operative pulmonary embolism. Since no embolic events were reported in association with use of placebo in this set of clinical studies, there is a potential connection with the use of E-TRANS fentanyl and opiate use in general. This should be noted in the label and practitioners should be aware that this was a delayed finding.

In one patient, whose past medical history was notable for chronic obstructive pulmonary disease and tobacco use, atelectasis and hypoxemia noted. It is unclear whether mild opiate-induced respiratory depression may have contributed to atelectesis in a patient with insufficient pulmonary reserves. This case may have been related to use of study medication. E-TRANS fentanyl may not be appropriate for patients with diminished pulmonary function.

During the placebo-controlled trials submitted in support of efficacy, more of the patients who received E-TRANS fentanyl 40 mcg reported at least one adverse event than those who received placebo: 69% versus 47%. In the active-controlled trial, 79% of the patients who received IV PCA morphine reported at least one adverse event. The most commonly reported adverse events during the placebo-controlled trials were nausea, application site reactions (erythema), emesis, fever and headaches.

Across all clinical studies, under 10% of patients experienced an episode of oxygen saturation of under 90%. While the incidence of oxygen desaturation episodes for patients using E-TRANS 40 mcg systems, 3%, was almost quadruple that of the patients who used E-TRANS placebo, 1%, the incidence was half that seen with use of intravenous morphine patient controlled analgesia (IV-PCA morphine), 6%.

B. Description of Patient Exposure

Demographics

The Integrated Summary of Safety (ISS) database, comprising patients, represented results from multiple studies. The majority of the patients (see Table 28 below) who participated in these studies were female (n=800, 60.1 %) and Caucasian, (n=2177, 61.9%).The studies were all completed at the time of NDA submission, therefore no additional safety information was provided in the 120 day update. ALZA exposed

patients to E-TRANS fentanyl in 25 mcg and 40 mcg doses. While the 40 mcg dose is the dose that is being submitted for marketing approval, the safety profile is based upon all exposures to E-TRANS fentanyl.

Table 28 :
Demographics for the ISS

TABLE G
Patient Demographics (Sex, Age, Race and Surgery Type) All Clinical Studies

	Treatment Group						
	E-TRANS® fentanyl 40 µg (n=1142)	E-TRANS® fentanyl 25 µg (n=785)	E-TRANS® fentanyl 25/40 µg (n=28)*	Placebo (n=321)	IV PCA Morphine (n=361)	IM Morphine (n=43)	All Patients (n=2660)
Sex							
Male	322 (28.2%)	277 (36.2%)	10 (35.7%)	90 (28.0%)	85 (23.5%)	16 (37.2%)	800 (30.1%)
Female	820 (71.8%)	488 (63.8%)	18 (64.3%)	231 (72.0%)	276 (76.5%)	27 (62.8%)	1860 (69.9%)
Age							
Mean (SEM)	50.3 (0.5)	45.4 (0.7)	12.3 (0.4)	52.1 (0.8)	49.2 (0.8)	48.9 (2.0)	48.6 (0.3)
Median (range)	49.0 (18, 90)	46.0 (5, 87)	13.0 (6, 16)	51.0 (18, 90)	47.0 (18, 88)	50.0 (19, 75)	48.0 (5, 90)
Race							
Caucasian	930 (81.4%)	646 (84.4%)	22 (78.6%)	275 (85.7%)	263 (72.9%)	41 (95.3%)	2177 (81.8%)
Black	103 (9.0%)	49 (6.4%)	4 (14.3%)	22 (6.9%)	73 (20.2%)	2 (4.7%)	253 (9.5%)
Asian	9 (0.8%)	2 (0.3%)	0	2 (0.6%)	4 (1.1%)	0	17 (0.6%)
Hispanic	43 (3.8%)	32 (4.2%)	2 (7.1%)	14 (4.4%)	17 (4.7%)	0	108 (4.1%)
Polynesian	48 (4.2%)	30 (3.9%)	0	6 (1.9%)	0	0	84 (3.2%)
Other	9 (0.8%)	6 (0.8%)	0	2 (0.6%)	4 (1.1%)	0	21 (0.8%)
Surgery Type							
Orthopedic bone	428 (37.5%)	411 (53.7%)	20 (71.4%)	136 (42.4%)	115 (31.9%)	21 (48.8%)	1131 (42.5%)
Upper abdominal	47 (4.1%)	53 (6.9%)	4 (14.3%)	12 (3.7%)	15 (4.2%)	0	131 (4.9%)
Thoracic/chest	25 (2.2%)	54 (7.1%)	2 (7.1%)	7 (2.2%)	4 (1.1%)	5 (11.6%)	97 (3.6%)
Lower abdominal	617 (54.0%)	167 (21.8%)	2 (7.1%)	162 (50.5%)	221 (61.2%)	16 (37.2%)	1185 (44.5%)
Neurologic	0	9 (1.2%)	0	0	0	0	9 (0.3%)
Other	25 (2.2%)	71 (9.3%)	0	4 (1.2%)	6 (1.7%)	1 (2.3%)	107 (4.0%)

* In pediatric Study C-2000-005, 28 patients were titrated up to E-TRANS® fentanyl 40 µg because of inadequate analgesia, as allowed per protocol, and are shown in the 25/40 µg group.
Source: Table 2.1

Subject disposition

ALZA exposed patients to E-TRANS fentanyl in 25 mcg and 40 mcg doses. I have combined all patients who received E-TRANS fentanyl into a single group. I have separated the control population into those who received placebo and those who received IV PCA morphine, the active control used in Study C-2000-007. I have reported the disposition of all participants treated during the development program, even those participants in studies that were discontinued prematurely due to suspected technical failures of the E-TRANS system.

The majority of the patients who received either E-TRANS fentanyl, intravenous morphine or intramuscular (IM) morphine completed the study. Only 27% of the patients who did not receive an opiate completed the study, see table 29 below.

Table 29:
Subject disposition

	E-TRANS fentanyl	E-TRANS placebo	IV morphine	IM morphine
Began treatment	**1935(100%)**	**321 (100%)**	**361 (100%)**	**44 (100%)**
Withdrawals	**384 (20%)**	**233 (63%)**	**97 (27%)**	**6 (14%)**
Deaths	0	0	0	0
Other adverse event	66	9	19	3
Withdrawn consent	32	4	5	0
Insufficient response	237	186	35	2
<3 hours	26	40	4	0
≥3 hours	211	146	31	2
Protocol violation	12	5	6	1
Technical failure	8	4	1	0
Other	29	25	31	0
Completed study	**1714(80%)**	**88 (27%)**	**264 (73%)**	**38 (86%)**

The majority of the study participants who were exposed to E-TRANS fentanyl 40 mcg systems were exposed for 24 hours or less, in contrast to participants who were exposed to E-TRANS fentanyl 25 mcg systems,see Table 30 below.

Table 30:
E-TRANS fentanyl exposure by time interval

Time Interval	Total	40 mcg	25 mcg
Number of subjects	1907	1142	765
<3 hours	36	28 (3%)	8 (1%)
≥3-24 hours	744	564 (49%)	180 (24%)
>24-≤48 hours	854	319 (28%)	535 (70%)
>48-<72 hours	243	206 (18%)	37 (5%)
>72 hours	30	25 (2%)	5 (1%)

The majority of the patients who used the E-Trans fentanyl 40 mcg system used a single system for an exposure of 24 hours or less and obtained, on average 30 doses, with a range of 0-88 doses.

Table 31:
E-TRANS fentanyl exposure (40 mcg) by time interval and estimated mean number of doses/patient

Time Interval	Total	Mean # of Doses (range)
Number of subjects	1142	
<3 hours	28 (3%)	6.9 (0-13)
≥3-24 hours	564 (49%)	30.4 (0-88)
>24-≤48 hours	319 (28%)	38.7 (0-163)
>48-<72 hours	206 (18%)	71.8 (13-225)
>72 hours	25 (2.2%)	80.4 (23-208)

C. Methods and Specific Findings of Safety Review

Summary

I performed a detailed review of the ISS submitted by ALZA, reading each submitted narrative and cross-referencing a subset of the reported adverse events with the case report forms provided. The case-report tables were reviewed.

No study site reported a patient dying while an E-TRANS system was in place. Five patients died after completing or withdrawing from the study. Three of these patients had deaths attributed to pulmonary embolism. The other two died of sepsis.

The majority of the serious adverse events reported were surgical complications such as wound infection or separation. There were episodes of myocardial infarction in patients who had cardiovascular abnormalities such as atherosclerotic coronary disease. These episodes were probably not related to use of study drug.

There were multiple reports of ileus, which was noted to occur at a higher incidence in patients receiving E-TRANS 40 mcg than in patients receiving placebo. Some of the reports of ileus occurred in conjunction with surgeries that would have involved bowel manipulation. In the latter instances it is unclear whether the decrease in bowel motility was in response to surgical manipulation of the gut or to the use of study drug. Fentanyl, as an opiate, is known to decrease bowel motility. The combination of opiate use and post-surgical immotility may have contributed to the duration and severity of ileus in some study participants.

A total of eight embolic events were reported in users of the E-TRANS system. Since no embolic events were reported in association with use of placebo in this set of clinical studies, there is a potential connection with the use of E-TRANS fentanyl and opioid use in general.

During the placebo-controlled trials submitted in support of efficacy, more of the patients who received E-TRANS fentanyl 40 mcg reported at least one adverse event than those who received placebo: 69% versus 47%. In the active-controlled trial, 79% of the patients who received IV PCA morphine reported at least one adverse event. The most commonly reported adverse events during the placebo-controlled trials were nausea, application site reactions (erythema), emesis, fever and headaches.

Deaths

The deaths described below all occurred after the E-TRANS system had been removed from the patient and the patient had been withdrawn from the study.

No patients died while the E-TRANS system was in place.

Patient 110 (Study C2000-006)
This 83 year old woman received E-TRANS fentanyl (25 mcg) following a bilateral salphingo-oophorectomy. She developed respiratory failure on postoperative day 3. She was thought to have died due to a pulmonary embolism.

Patient 125 (Study C93-023)
This 63 year old man received E-TRANS fentanyl (25 mcg) following a total hip replacement. His recovery was described as uneventful . One week after discharge, he returned to the hospital with chest pain and dyspnea. He was thought to have had a pulmonary embolism which led to his demise.

Patient 1212 (study C-2001-011)
This 79 year old man received E-TRANS fentanyl (40 mcg) following repair of a ventral hernia which had developed after repair of an abdominal aortic aneurysm. Approximately three hours after application of the E-TRANS system, he withdrew from the study due to inadequate analgesia.

On postoperative day two (POD 2), his oxygen requirements increased. The day before, POD 1, he had been receiving 2L/min oxygen by nasal cannula and maintaining an oxygen saturation of 94%. On POD 2, he was placed on 100% oxygen by non-rebreather mask. He was noted to have bilateral atelectasis with a possible left lower lobe infiltrate, and tachycardia with occasional premature ventricular contractions. A ventilation/perfusion scan was scheduled to evaluate for potential pulmonary embolism. Just prior to transport to radiology, the patient stood up to use the toilet. After complaining of shortness of breath, he became cyanotic and apneic. Cardiopulmonary resuscitation was started with conversion from electromechanical dissociation to ventricular tachycardia. After defibrillation, he became asystolic. He received atropine, epinephrine, sodium bicarbonate, vasopressin and calcium chloride. He was pronounced dead after 31 minutes of attempts at resuscitation. It is unclear whether study drug contributed to his demise.

Patient 30235 (study C-94-058)
This 64 year old man received E-TRANS fentanyl (40 mcg) following sigmoid colon resection. During his 72 hours on study , he had three adverse events: back pain, headache and application site erythema. Three days after study completion, he was noted to have fecal emesis. Exploratory surgery revealed a ruptured diaphragm and esophagus with fecal matter present in the peritoneal and pleural spaces. His death two weeks later was attributed to septic shock. This event appears to have been related to surgical complications and does not appear to have been related to study drug.

Patient 30598 (study C-94-058)
This 66 year old man received E-TRANS fentanyl (40 mcg) following a total knee arthroplasty. During his 39 hours on study, he became psychotic which led to the study treatment being discontinued. Over 4 weeks later, he remained psychotic. He developed sepsis and pneumonia and subsequently died due to multi-system organ failure.

Serious Adverse Events (SAE)

The majority of the SAE reported were surgical complications e.g. wound infections, wound separations. These episodes were probably not related to use of study drug.

There were episodes of myocardial infarction in patients who had cardiovascular abnormalities such as atherosclerotic coronary disease. These episodes were probably not related to use of study drug.

There were multiple reports of ileus, which was noted to occur at a higher incidence in patients receiving E-TRANS 40 mcg than in patients receiving placebo. Some of the reports of ileus occurred in conjunction with surgeries that would have involved bowel manipulation. In the latter instances it is unclear whether the decrease in bowel motility was in response to surgical manipulation of the gut or to the use of study drug. Fentanyl, as an opiate is known to decrease bowel motility. The combination of opiate use and post-surgical immotility may have contributed to the duration and severity of ileus in some study participants

There were 7 reports of pulmonary emboli in patients who received analgesia from the E-TRANS fentanyl system.

- Patient 125 (C93023), Patient #110 (C-2000-006) and Patient #1212 (C-2001-011) were described under deaths
- Patient 306 (C-2000-008), a 44 year old woman, received E-TRANS fentanyl after an abdominal hysterectomy performed on —. She completed 24 hours on study drug. Two days later, a pulmonary embolism was detected and anticoagulation was started
- Patient 1032 (C-95-016), a 47 year old woman , received E-TRANS fentanyl after an abdominal hysterectomy performed on —. She completed 24 hours on study drug. On April 5 1997, she became symptomatic from a pulmonary embolism.
- Patient 1070 (C-95-016), a 48 year old woman, received E-TRANS fentanyl after an abdominal hysterectomy performed on —. She completed 24 hours on study drug, after receiving 60 mcg of intravenous fentanyl as rescue medication. On July 9 1997, a pulmonary embolism was detected.
- Patient 30094 (C-94-059), a 54 year old man received E-TRANS fentanyl after a right inguinal hernia repair and varicose vein ligation in the left leg on —. He was noted to have developed a pulmonary embolism on February 22 1998.

There was 1 report of pulmonary embolus in a 52 year old woman who received IM morphine, Patient 30406 (study C94058). She was on therapy for 14.7 hours. Her embolism occurred on postoperative day 10.

There was 1 report of pulmonary embolus in a 68 year old woman who received IV morphine, Patient 116 (study C2000-007). She was on therapy for 72 hours. Her embolism occurred at hour 55.

There were no reports of pulmonary embolism in patients who received placebo therapy.

Additional serious adverse events of note

- A 35 year old woman (pt 2220, C-2000-007) received E-TRANS fentanyl following an abdominal hysterectomy on —. On the day of system placement, she had nausea, vomiting and loss of consciousness during a venipuncture, from which she recovered without medical intervention. She did not complete 24 hours on the system due to an adverse event. She was noted to have decreased awareness during her 0530 assessment on —. The E-TRANS system was removed at 0545. At 0600, she was unresponsive so she was given 0.4 mg of Narcan. At 0615, she turned her head to the right with her eyes rolled up, vomited and became unresponsive. (*Reviewer's note-Her level of responsiveness after the first dose of Narcan is unclear.*) At 0630, Narcan was given with no response. Her vital signs at the time were HR 72 bpm, RR 20 bpm, B/P 105/70. At 0645, resuscitation was initiated due to respiratory arrest. She was intubated during the resuscitation and extubated the same day. An MRI performed on — revealed a right thalamic lesion, left occipital infarct and multiple posterior circulatory infarcts all of which was thought to be consistent with embolic stroke. Angiography performed on — revealed a left vertebral artery occlusion with a possible underlying dissection so she began therapy with warfarin. Since no embolic events were reported in association with use of placebo in this set of clinical studies, there is a potential connection with the use of E-TRANS fentanyl and opioid use in general. It is not possible to be more definitive since we do not know the baseline rate for postoperative embolic events.

- There was a report of paranoia and suicidal ideation in a 60 year old female (patient 1319, study C-2000-008), with a history of angina and paranoia, who had a right hemicolectomy on —. She did not complete the 24-hour study period due to inadequate analgesia from the E-TRANS fentanyl system. Two days after beginning the study, on —, she was discovered to have had an acute inferior wall myocardial infarction. While in the coronary care unit, she was noted to be paranoid and delusional with suicidal ideation. While this alteration in mental status may have been related to use of opioids, no clear relation may be drawn since the patient was known to have a history of paranoia prior to beginning use of the study medication. The myocardial infarction is unlikely to have been related to use of fentanyl.

- There was a report of confusion, agitation and tangential communication in a 66 year old male (Pt 133, Study C-2000-007) with a past medical history notable for increasingly frequent episodes of anxiety, fear, depressed mood and suicidal ideation. He had an E-TRANS fentanyl system placed on —, after a lumbar laminectomy. The system was removed on — when he was noted to be confused and agitated. He was empirically treated for meningitis, no lumbar puncture was performed. No significant findings were discovered by the infectious disease consultant or the neurological consultant called to evaluate the patient. The patient gradually improved and was discharged on — The investigator

reported that this event may have been related to study medication. I would concur with that assessment.

- A 74 year old woman (patient 1304, study C-2001-011) with past medical history notable for COPD, 50 years of tobacco use, and hypertension, began the 24-hour study period with the E-TRANS fentanyl system after a hemicolectomy on —. On — she had exacerbation of her COPD oxygen saturation of 89% on room air. Her arterial blood gases were pH 7.36, pCO2-55.2 mm HG, pO2- 52 mm HG and O2 of 85%. On the same day she was noted to have fluid overload which responded to Lasix as well as left bundle branch block which did not require treatment. Her hypoxemia was treated with oxygen *(Reviewer's note: The manner of delivery was not specified)*, pulmonary toilet, albuterol and ipratropium inhalers. Due to continued atelectasis with hypoxemia unresponsive to nebulizer treatments, bronchoscopy was performed. After suctioning of mucous plugs from both lower lobes the patient recovered and was able to be discharged three days later. The investigator reported that the events were unrelated to study medication. It is unclear that this is the case since mild opiate-induced respiratory depression may have contributed to atelectesis in a patient with insufficient pulmonary reserves. This case may have been related to use of study medication

- A 49-year-old female (pt 1115, C-2000-008) received E-TRANS placebo after repair of an enterocutaneous fistula. She was discontinued from the study due to use of Toradol for back pain. After study discontinuation, she was noted to be hypoxic and dyspneic. She was subsequently noted to have adult respiratory distress syndrome and pleural effusion among other medical complications.

- A 66 year old female (pt 708, C-2000-007) received IV PCA morphine following a left total hip replacement. She discontinued the study due to pain with need for rescue analgesics. She had an acute middle cerebral artery cerebrovascular accident. During evaluation, she was found to have left internal artery stenosis as well as right carotid artery narrowing.

- An 82 year old female (pt 2002, C-2000-007) received IV PCA morphine following a colonic resection with removal of a mass. The PCA was removed when she was noted to be confused, disorientated and agitated. She was found to have congestive heart failure with hypoxia.

- An 77 year old female (pt 2903, C-2000-007) received IV PCA morphine following a knee replacement and ganglionectomy. She had received 15 mg of intravenous morphine prior to beginning treatment with the PCA. Within one hour she was noted to be drowsier, with a respiratory rate of 12 breath/minute. Three hours after that observation, she was noted to have a respiratory rate of 4 breaths a minute. Narcan was administered. She was continued on IV PCA with morphine on-demand and Narcan added to the IV fluids.

- An 71 year old male (pt 3603, C-2000-007) received IV PCA morphine following a knee replacement. He did not require rescue medication and was able to complete all 72 hours on study. The day after study completion, a doppler ultrasound revealed an acute non-occluding thrombus in the right posterior tibial vein extending into the tibioperoneal trunk.

Discontinuations due to adverse events

Of the 2660 participants in these clinical studies, 100 discontinued due to adverse events, 3.6%.

The discontinuation rate for AEs in the E-TRANS fentanyl group was 3.4%, 66 of the 1935 patients who received the investigational medication withdrew, see appendices C and D for patient listings.

The discontinuation rate for AEs in the E-TRANS placebo group was 2.8%, 9 of 321 patients withdrew, see appendices C and D for patient listings.

The discontinuation rate for AEs in the morphine group was 5.4%, 22 of the 404 patients withdrew, see appendices C and D for patient listings.

Adverse events

While the safety profile is based upon all exposures to E-TRANS fentanyl, the 40 mcg dose is the dose that is being submitted for marketing approval. The adverse events data presented below is from the study participants who used the higher dose systems. While the incidence of adverse events with use of the 25 mcg E-TRANS system might be lower than that seen with the 40 mcg system, the 40 mcg system is the one proposed for marketing. If I were to combine the adverse event findings from the use of the 25 mcg E-TRANS system with those of the proposed marketed dose, this might dilute the 40 mcg adverse event profile.

During the placebo-controlled trials submitted in support of efficacy, more of the patients who received E-TRANS fentanyl 40 mcg reported at least one adverse event than those who received placebo: 69% versus 47%. In the active-controlled trial, 79% of the patients who received IV PCA morphine reported at least one adverse event. The most commonly reported adverse events during the placebo-controlled trials were nausea, application site reactions (erythema), emesis, fever and headaches.

The incidence of adverse events is higher in those patients who received higher amounts of fentanyl in the first 24 hours of therapy as may be seen from a review of the data presented in table 32. The majority of the patients used sixty or fewer doses in the first 24 hours, a total of $\leq$ 2400 mcg. Approximately 10% of the patients used more than 2400 mcg in the first 24 hours.

None of the patients who used the E-TRANS fentanyl 40 mcg system had clinically relevant respiratory depression (CRRD), defined as simultaneous bradypnea and excessive sedation, noted. Only one person with CRRD was reported , a participant who had been randomized to IV PCA morphine.

With the exception of the application site reactions seen, the most commonly reported adverse events i.e. nausea, vomiting were all effects expected from opiate usage. In light of the multiple reports of infected surgical sites, the incidence of fever is not unexpected.

There was no apparent increase in adverse events seen as the duration of wear was increased from 24 hours to 48 hours and even extended to 72 hours in some studies, see appendix D.

Table 32:
AE reported in >2% in all clinical studies of 40 mcg E-TRANS systems, divided by the number of doses received within the first 24 hours*

	Total patients using E-TRANS 40 mcg (n=1142)	***≤60 doses (n=1030)***	***>60 doses (n=111)***	**Placebo (n=321)**
Body as a whole				
Fever	200 (18%)	*179 (17%)*	*21 (19%)*	34 (11%)
Headache	165 (14%)	*143 (14%)*	*22 (20%)*	21 (7%)
Abdominal Pain	66 (6%)	*58 (6%)*	*8 (7%)*	5 (2%)
Back pain	47 (4%)	*38 (4%)*	*9 (8%)*	11 (3%)
Pain	28 (3%)	*27 (3%)*	*1 (1%)*	3 (1%)
Cardiovascular				
Hypotension	33 (3%)	*31 (3%)*	*2 (2%)*	2 (1%)
Hypertension	27 (2%)	*25 (2%)*	*2 (2%)*	5 (2%)
Digestive				
Nausea	511 (45%)	*453 (44%)*	*57 (51%)*	81(25%)
Vomiting	198 (17%)	*177 (17%)*	*21 (19%)*	19 (6%)
Nausea and vomiting	35 (3%)	*30 (3%)*	*5 (5%)*	2(1%)
Constipation	28 (3%)	*24 (2%)*	*4 (4%)*	2(1%)
Hematologic				
Anemia	52 (5%)	*44 (4%)*	*8 (7%)*	3 (1%)

Table 32:
AE reported in >2% in all clinical studies of 40 mcg E-TRANS systems, divided by the number of doses received within the first 24 hours*

	Total patients using E-TRANS 40 mcg (n=1142)	***≤60 doses (n=1030)***	***>60 doses (n=111)***	**Placebo (n=321)**
Nervous				
Dizziness	78 (7%)	*74 (7%)*	*4 (4%)*	4 (1%)
Insomnia	31 (3%)	*27 (3%)*	*4 (4%)*	17 (5%)
Hypertonia	25 (2%)	*17 (2%)*	*8 (7%)*	1 (0.3%)
Somnolence	22 (2%)	*19 (2%)*	*3 (3%)*	0
Anxiety	16 (1%)	*13 (1%)*	*3 (3%)*	6 (2%)
Respiratory				
Hypoxia	30 (3%)	*23 (2%)*	*7 (6%)*	2(1%)
Dermatologic system				
ASR**	206 (18%)			15 (5%)
Pruritis	89 (8%)	*72 (7%)*	*17 (15%)*	1 (0.3%)
Wound site bleeding	25 (2%)	*24 (2%)*	*1 (1%)*	2(1%)
Diaphoresis	17 (2%)	*14 (1%)*	*3 (3%)*	0
Urogenital system				
Urinary retention	41 (4%)	*32 (3%)*	*9 (8%)*	2(1%)

*AEs reflect all AEs experienced during the trial, not just the first 24 hours
** Application Site Reaction (ASR), e.g erythema, vesicles or pruritis
(Sources: Sponsor provided ISS, tables 9.1 and 37.1)

Adverse events of special interest

Erythema

Skin-site assessments, including erythema, were coded on case report forms separate from other adverse events. Evaluation of the available data from all of the clinical studies using E-TRANS fentanyl revealed that approximately one third of the patients had detectable erythema at the application site. In patients 139 and 142 from Study 95-019, hyperpigmentation at the application site lasted two to three weeks. This finding was coded as application site reaction-postinflammatory. Patients 3113, 3116 and 3117 from Study C-2000-007 noted a residual effect rectangular scar at the application site at 1 to 3 months after study completion. This finding was coded as application site reaction-other.

In all the clinical studies, elderly patients were seen to have less erythema than younger adults, 40% versus 51%. As in the younger adults, most of the erythema reported in the elderly was barely perceptible/noticeable redness. In the pediatric population, erythema to any degree was more common than in adults, 72% of patients who received 25 mcg systems and 79% of those patients who received 40 mcg systems as compared to 60 % of

adults. Unlike adults, the most common application site reaction seen in pediatric patients was vesicles or "transient microblisters."

Table 33:
Number of patients with erythema

	E-TRANS fentanyl 40 mcg n=1167	Placebo n=316
None	465 (40%)	262 (83%)
Barely perceptible/noticeable redness	351 (30%)	41 (13%)
Definite/well defined redness	314 (27%)	10 (3%)
Beet redness	35 (3%)	3 (1%)

Clinically relevant respiratory depression (CRRD)
In most studies this was defined as excessive sedation accompanied by bradypnea (respiratory rate less than 8 breaths per minute sustained for one minute). The evaluation for this adverse event included assessment of the need for medical intervention, oxygen saturation and vital signs.

In all studies done in the pediatric population, this was defined as less than 12 breaths per minute for patients ages 6 through 8 years inclusive or 10 breaths per minute for patients aged 9 and older.

The only reported case of CRRD occurred on study C-2000-007, involving a patient who was receiving IV PCA morphine.

Hypoxia/hypoxemia
The sponsor sorted the reported oxygen saturation levels into 5 groups: ≥95%, 93% to <95%, 90 to <93%, 88% to 90%, and <88%.

Across all clinical studies, under 10% of patients experienced an episode of oxygen saturation of under 90%. While the incidence of oxygen desaturation episodes for patients using E-TRANS 40 mcg systems was almost quadruple that of the patients who used E-TRANS placebo or E-TRANS 25 mcg, the incidence was half that seen with use of intravenous morphine patient controlled analgesia (IV-PCA morphine).

Table 35:
Percentage of patients with oxygen saturation less than 90% during clinical studies

Treatment group	Percentage of patients with oxygen saturation < 90%
E-Trans fentanyl 25 mcg	1%
E-Trans Placebo	1%
E-Trans fentanyl 40 mcg	**3%**
E-Trans fentanyl 25/40 mcg	4%
IV PCA morphine	6%
IM morphine	0%

D. Adequacy of Safety Testing

The adverse event profile of fentanyl is well-characterized since the drug is currently marketed in formulations for transmucosal, transdermal and intravenous administration. The major issue for this product, E-TRANS, was the safety of iontophoretic delivery of fentanyl.

Routine laboratory testing and electrocardiograms were not incorporated into the clinical studies but they did not need to be since they would not have been expected to provide additional new information on the adverse event profile to be expected with fentanyl use.

The patient population selected for the clinical studies was appropriate. Initially, the development plan included studies in the pediatric population but that part of the plan was discontinued when ALZA began focussing on the E-TRANS 40 mcg system.

There were two documented instances where the patient's family was administering the doses instead of the patient. In both cases the patients experienced an adverse event. In one case the patient. who had been using a 40 mcg system, developed hypoxia with an oxygen saturation of 91%. This episode resolved with naloxone therapy. While misuse of patient-controlled analgesia by family members or others administering the on-demand dosing instead of the patient is a known occurrence and is not specific to E-TRANS usage, the device administering the analgesic is supposed to have built-in safeguards against administering more than a specified amount of drug in a given amount of time. In study C-2000-006, Patient 803's family was administering the on-demand dosing instead of the patient. According to ALZA, the patient was estimated to have received 113 doses of 25 mcg fentanyl, with the use of two E-TRANS systems. This patient had somnolence, which could be related to the use of study drug reported as a serious adverse event.

E. Summary of Critical Safety Findings and Limitations of Data

The adverse event profile of fentanyl is well-characterized since the drug is currently marketed in formulations for transmucosal, transdermal and intravenous administration.

The majority of the serious adverse events reported were surgical complications such as wound infection or separation. There were episodes of myocardial infarction in patients who had cardiovascular abnormalities such as atherosclerotic coronary disease. These episodes were probably not related to use of study drug.

There were multiple reports of ileus, which was noted to occur at a higher incidence in patients receiving E-TRANS 40 mcg than in patients receiving placebo. Some of the reports of ileus occurred in conjunction with surgeries that would have involved bowel manipulation. In the latter instances it is unclear whether the decrease in bowel motility was in response to surgical manipulation of the gut or to the use of study drug. Fentanyl, as an opiate is known to decrease bowel motility. The combination of opiate use and

post-surgical immotility may have contributed to the duration and severity of ileus in some study participants.

During the placebo-controlled trials submitted in support of efficacy, more of the patients who received E-TRANS fentanyl 40 mcg reported at least one adverse event than those who received placebo: 69% versus 47%. In the active-controlled trial, 79% of the patients who received IV PCA morphine reported at least one adverse event. The most commonly reported adverse events during the placebo-controlled trials were nausea, application site reactions (erythema), emesis, fever and headaches. With respect to this specific method of drug delivery, over 50% of the patients had erythema and/or pruritis at the E-TRANS application site. These findings are related to use of the E-TRANS system and should be addressed in the labeling.

A total of eight embolic events were reported in users of the E-TRANS system. Since no embolic events were reported in association with use of placebo in this set of clinical studies, there is a potential connection with the use of E-TRANS fentanyl and opioid use in general. This should be noted in the label and practitioners should be aware that this was a delayed finding.

While the system is not expected to interfere with common electrical devices such as cellular telephone and typical medical/therapeutic equipment, magnetic resonance imaging devices may damage the system. Additionally, the system is not compatible with cardioversion or defibrillation due to the electromagnetic fields produced which render the E-TRANS incapable of iontophoretic fentanyl release of. Radiopaque components within the system may interfere with x-ray, or CAT scan images. This information should be included in the labeling and be conveyed to the practitioners.

The safety testing done for the drug moiety, fentanyl, was adequate however, further characterization of the device failure rate is important. It may be expected that there will be a certain amount of device misuse by persons other than the patient administering the on-demand dosing. If the patient were to be the only one administering on-demand doses, he/she would stop administering the doses if he/she were to become somnolent due to the opiate. A misguided but well-meaning family member may administer additional doses in an effort to make certain that their relative is pain-free while he/she is sleeping, having mistaken a brief arousal for an expression of pain. If the automatic shut-off mechanism incorporated into E-TRANS fails, the patient could receive a fentanyl overdose with possible fatal consequences.

VIII. Dosing, Regimen, and Administration Issues

Choice of dose/dosing limits

FEN-INT-006 (see table 36 below, see appendix B for details) was a multi-center, randomized, double-blind, parallel group dose-ranging study to prove the superiority of 40 mcg fentanyl over 20 mcg fentanyl in patient controlled analgesia and compare the

safety of fentanyl at 20 mcg (maximum of 80 mcg/hour), 40 mcg (maximum of 240 mcg/hour), and 60 mcg (maximum of 360 mcg/hour).

Demands for medication during lockout periods, which was used as a surrogate for patient discomfort and desire for increased analgesia, was seen more frequently in the patients receiving 20 mcg on-demand doses (median 55 demands) as compared to the 40mcg on demand (median 28 demands) and 60 mcg on demand (median 26 demands) groups.

The investigators reported that adverse respiratory events were more frequent and more severe in patients receiving 60 mcg on demand doses compared to 40 mcg on demand doses. This study supported the choice of 40 mcg as the optimal on-demand dose.

Study C-93-023 which compared safety and efficacy of the 25 mcg and the 40 mcg E-TRANS systems showed similar safety with better pain control from the higher dose (see table 37 below, see appendix B for details). This study provided guidelines for the maximum opioid requirements in patients treated for postoperative pain, 80 doses of 40 mcg appeared sufficient to treat most patients.

In the placebo-controlled studies, only 1.1% of the evaluable patients (those who were studied for more than 3 hours) used all 80 doses within the 24 hour period. When all controlled studies were reviewed, on average under 40 doses were used in the first 24 hour period with highest dose use seen in the first 2 hours after beginning the study.

The clinical studies performed did not establish an opiate conversion scheme for patients who begin use of oral opiates after use of the E-TRANS device.

Table 36:
Summary of dose finding study FEN-INT-6[a]

	Dose		
	20 mcg	40 mcg	60 mcg
Mean serum fentanyl concentrations (ng/mL)	0.7-1.2	1.0-1.2	1.0-1.6
# of doses delivered/24 treatment period	51.8	41.1	35.7
Incidence of respiratory system AE			
Bradypnea	0	0	6%
Respiratory insufficiency	0	0	4%
Respiratory depression[b]	0	2%	2%
Hypoxia	0	2%	0

[a]This table is a modification of Table T in the NDA Submission's Integrated Summary of Efficacy.
[b]This AE was reported for one patient in the 40 mcg group (moderate intensity) and one patient in the 60 mcg group (severe intensity). In both cases the AE led to study discontinuation.

Table37:
Summary of dose confirmation study C-93-023[a]

Dose	25 mcg	40 mcg
# of doses delivered/24 treatment period	56.9	38.7
Percentage of patients requiring supplemental fentanyl		
0-3 hours	81%	46%
3-6 hours	27%	4%
6-24 hours	19%	3%
Hypoventilation	1.3%	1.1%
Dyspnea	2.5%	0.6%
Clinically relevant respiratory depression	0	0
Hypoxia	6.3%	2.9%

[a]Table 37 is a modification of Table U in the NDA Submission's Integrated Summary of Efficacy.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

The majority of the participants in the clinical studies of the E-TRANS system were female (72.5%). There was no evidence of gender effect on efficacy. The incidence of adverse events was higher in females, 79% versus 69%.

In Study C-2001-011, E-TRANS 40 mcg system was found to demonstrate a positive effect on pain relief compared to placebo during a subgroup analysis done by gender. The other studies did not confirm this finding due to insufficient numbers in the placebo group (C-95-016) or inconsistent results (C-2000-008).

Table 38:
Adverse events by gender (all clinical studies)

	Females (n=820)	Males (n=322)
Nausea	416 (51%)	95 (30%)
Vomiting	162 (20%)	36 (11%)
Fever	137 (17%)	63 (20%)
Headache	146 (18%)	19 (6%)

Modification of sponsor table W from the ISS, based on ISS tables 34.1 and 34.2

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

Age

Over 500 elderly patients (persons 65 years or older) participated in these studies. 256 of them used E-TRANS 40 mcg systems. Sixty-nine of the E-TRANS 40 mcg users were between the ages of 75 and 90 years old. The demographics in the elderly subset mirrored

that of the larger study population in that the majority were female (59.4%) and Caucasian (89.5%).

In Study C-2001-011, E-TRANS 40 mcg system was found to demonstrate a positive effect on pain relief compared to placebo during a subgroup analysis done by age. The other studies did not confirm this finding due to insufficient numbers in the placebo group (C-95-016) or inconsistent results (C-2000-008).

Almost half of the 256 elderly adults over 65 years who were exposed to 40 mcg E-TRANS systems were exposed for 24 hours or less: 6 (2%) were exposed for under 3 hours; 108 (42%) were exposed for 3-24 hours; 73 (29%) were exposed for 24-48 hours; 58 (23%) were exposed for 48-72 hours; 11 (4%) were exposed for more than 72 hours. The estimated mean number of doses per time period were similar to those seen in the general study population.

The adverse event profile for the elderly was similar to that of the participants under age 65 years with the most commonly reported adverse events being nausea, vomiting, fever and headache. The incidence of fever was slightly higher in the elderly, 22% as opposed to 16%, but the incidences of the other three adverse events was higher in the younger adults.

Race/ethnicity

The majority of the participants in these studies were Caucasian (79%). The White patients who received an opiate (fentanyl, or morphine) reported a higher incidence of adverse events than Blacks who received an opiate (fentanyl or morphine) did, 77% versus 67%. Skin-site assessment were coded separately from the other adverse events. The incidence of application site erythema was higher in Whites. The latter finding may have been due to ascertainment bias, since mild erythema may be more difficult to appreciate on persons with darker skin pigmentation.

Table 39:
Adverse effects by ethnicity (all clinical studies)

	Whites (n=930)	Blacks (n=103)
Nausea	439 (47%)	31 (30%)
Vomiting	172 (19%)	8 (8%)
Fever	160 (17%)	16 (16%)
Headache	149 (16 %)	6 (6%)
ASR-pruritis	70 (8%)	7 (7%)

Modification of sponsor table X from the ISS, based on ISS tables 35.1 and 35.2

C. Evaluation of Pediatric Program

Inducers of this system may be expected to increase the systemic clearance and decrease opioid effects potentially including analgesia.

ALZA did a subgroup analysis to evaluate the frequency and types of adverse events seen in the 77 study participants whose histories indicated probable renal or hepatic impairment. This group included persons with end-stage renal disease, liver transplant, cirrhosis and hepatitis among other conditions. Serious adverse events (SAE) were experienced by eight of these patients (10%): 7 of whom had received E-TRANS 40 mcg systems; 1 of whom had received IV PCA morphine. The incidence of SAE in this specific subpopulation is higher than that seen in the overall study population. Overall 48 (4%) of the 1142 patients who used E-TRANS fentanyl had an SAE, 7 of those patients were in the subpopulation of patients with probable renal or hepatic impairment. Overall 13 (4%) of the 361 patients who used IV PCA morphine had an SAE, 1 of those patients was in the subpopulation of patients with probable renal or hepatic impairment.

Since fentanyl may cause hypoventilation, this product should be used cautiously in patients with conditions that predispose them to hypoventilation e.g. chronic obstructive pulmonary disease. Practitioners should give careful consideration to use of this product in patients with conditions that predispose them to retention of carbon dioxide, e.g. patients with increased intracranial pressure.

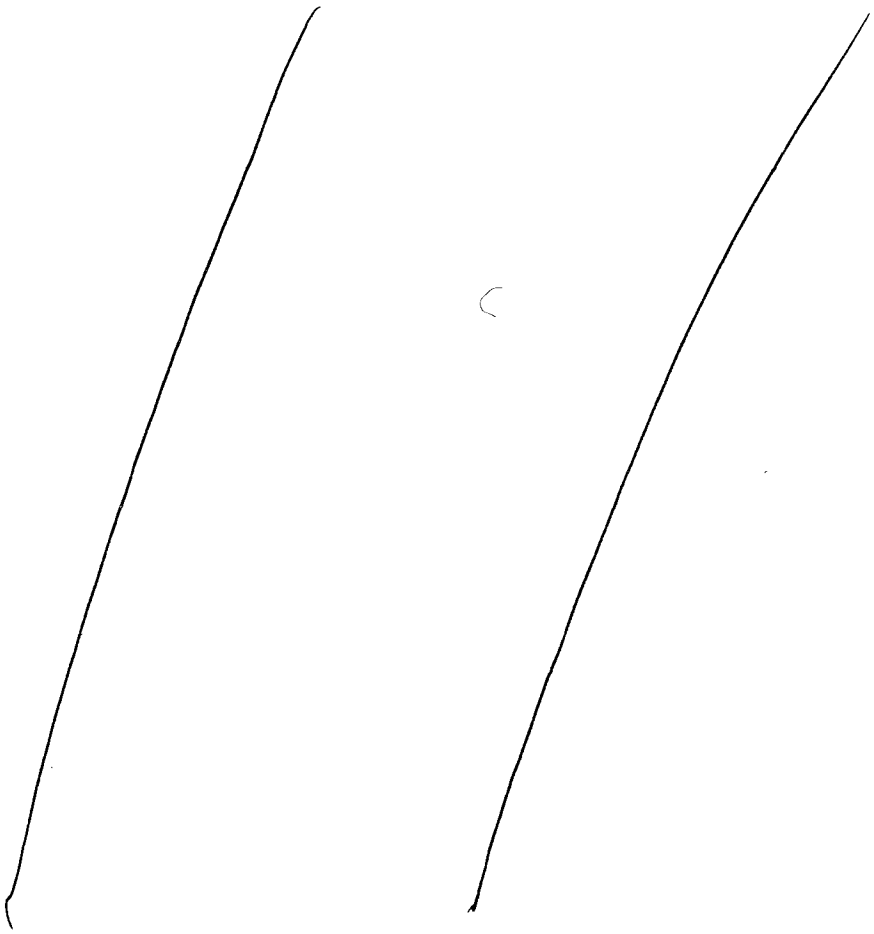
X. Risk management plan

ALZA plans to distribute this product to hospital
with labeling restricting use to ALZA expects E-TRANS will be classified as a Schedule II controlled substance. The product will have a bolded warning stating that contact with or oral ingestion of the hydrogels may cause hypoventilation or death.

For 12 months after initial launch, ALZA has proposed that non-working systems be returned to the company where a sample of the returned units will be analyzed for cause of failure.

ALZA developed a risk management plan for this product. The identified risks included patient overdose, improper patient selection, abuse/misuse/diversion by health care professional or others, exposure to fentanyl due to improper manipulation of the system or deliberate tampering with the system.

The risk management plan includes



XI. Conclusions and Recommendations

A. Conclusions

The E-TRANS (fentanyl HCL) patient-controlled transdermal system is an iontophoretic device, which uses low-level electricity to send fentanyl transdermally into the systemic circulation. E-TRANS is only suitable for use for a 24 hour period in patients who have been successfully titrated to comfort postoperatively and who have access to intravenous analgesia for the first three hours of device use, the period of skin equilibration.

ALZA submitted four trials in support of efficacy, three of which were placebo-controlled. The fourth trial used intravenous placebo-controlled morphine (IV PCA) as an active comparator. The hydrogel formulation, electronics design and housings of the E-TRANS fentanyl systems used in the Phase 3 clinical trials were identical to the systems that ALZA intends to market. The placebo systems were identical to the proposed

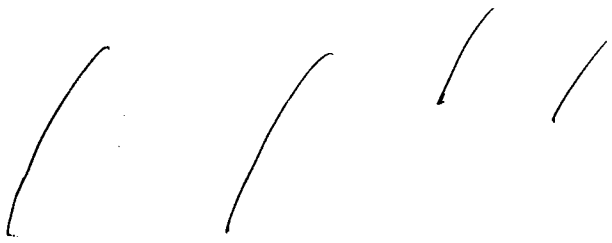
commercial systems except for the lack of the electrical current path to provide iontophoretic drug delivery.

Placebo-controlled studies C-95-016 and C-2000-011 demonstrated efficacy of the E-TRANS fentanyl system in patients who are at least three hours post surgery and have been successfully titrated to comfort with parenteral opioids. If the total IV opioid requirement for titration to comfort approaches the equivalent of 40 mg morphine sulfate or 400 mcg fentanyl, the patient should be reassessed to determine suitability for PCA opioid as a sole analgesic agent.

Placebo-controlled study C-2000-008 also demonstrated efficacy of the E-TRANS fentanyl system though with borderline results. The results from active-controlled study C-2000-007 were also borderline.

This device appears to have what is best described as a priming phase, i.e. the first 18-20 doses delivered are under the nominal 40 mcg dose, which would explain the study finding that the use of rescue analgesics was comparable in the two groups during the first 3 hours. It should be noted that after about the 40th dose, the device delivers, *in vivo*, about 44 mcg per dose, a 10% increase over the nominal dose. While the studies show that the effective analgesic dose for iontophoretic delivery of fentanyl lies somewhere between 25 and 40 mcg, it is not clear at what dose analgesia may reliably begin to be noted. Indeed this is probably a matter of individual variation. ALZA has satisfactorily demonstrated that after a period of non-use, e.g. if a patient were to sleep for 6-8 hours then re-activate the device, another equilibration phase would not be needed. An equilibration phase is only needed upon initial placement of the system. If a second device is worn, the residual serum level of fentanyl from the first system appears to be sufficient to provide analgesia for the equilibration phase needed for the second device.

ALZA reported that 8% (72/854) of the E-TRANS systems used in the placebo-controlled trials had suspected technical failures and 4% (22/590) of the E-TRANS systems used in the active-controlled trial submitted in support of efficacy had suspected technical failures. The types of E-TRANS malfunctions described in the study reports were as follows:



ALZA reports that modifications in the as well as modifications to the were made in response to the more commonly reported malfunctions. The adhesion issues were not amenable to modification in the adhesive formulation since alterations in adhesion characteristics can be partially related to aspects of individual

patient skin. At the present time, we are told that the "out of the box" failure rate may be expected to be around — at — . The sponsor has proposed a testing scheme to be done prior to administering the device to a patient. The feasibility of performing this testing in a clinical setting remains to be determined. The logistics of storing and returning defective devices to ALZA have yet to be determined.

The adverse events profile seen during the submitted trials was consistent with that seen with other fentanyl transdermal products. The major difference between this product and the currently marketed fentanyl transdermal products is that E-TRANS is indicated for acute use, including use in postoperative patients. The currently marketed transdermal products are specifically contraindicated in the postoperative period.

The majority of the serious adverse events reported were surgical complications such as wound infection or separation. There were multiple reports of ileus, which was noted to occur at a higher incidence in patients receiving E-TRANS 40 mcg than in patients receiving placebo. Some of the reports of ileus occurred in conjunction with surgeries that would have involved bowel manipulation. In the latter instances it is unclear whether the decrease in bowel motility was in response to surgical manipulation of the gut or to the use of study drug. Fentanyl, as an opiate is known to decrease bowel motility. The combination of opiate use and post-surgical immotility may have contributed to the duration and severity of ileus in some study participants.

A total of eight embolic events were reported in users of the E-TRANS system. A 35-year-old patient was noted to have had an embolic stroke, a finding that may or may not be related to the reports of pulmonary embolism. However, since no embolic events were reported in association with use of placebo in this set of clinical studies, there is a potential connection with the use of E-TRANS fentanyl and opiates in general. This should be noted in the label and practitioners should be aware that this was a delayed finding.

During the placebo-controlled trials submitted in support of efficacy, more of the patients who received E-TRANS fentanyl 40 mcg reported at least one adverse event than those who received placebo: 69% versus 47%. The most commonly reported adverse events during the placebo-controlled trials were nausea, application site reactions (erythema), emesis, fever and headaches. Across all clinical studies, under 10% of patients experienced an episode of oxygen saturation of under 90%. With respect to this specific method of drug delivery, 60% of patients noted erythema and/or pruritis at the E-TRANS application site.

In one patient, whose past medical history was notable for chronic obstructive pulmonary disease and tobacco use, atelectasis and hypoxemia noted. It is unclear whether mild opiate-induced respiratory depression may have contributed to atelectesis in a patient with insufficient pulmonary reserves. E-TRANS fentanyl may not be appropriate for patients with diminished pulmonary function

ALZA did a subgroup analysis to evaluate the frequency and types of adverse events seen in the 77 study participants whose histories indicated probable renal or hepatic impairment. This group included persons with end-stage renal disease, liver transplant, cirrhosis and hepatitis among other conditions. Serious adverse events (SAE) were experienced by eight of these patients (10%): 7 of whom had received E-TRANS 40 mcg systems; 1 of whom had received IV PCA morphine. The incidence of SAE in this specific subpopulation is higher than that seen in the overall study population. Overall 48 (4%) of the 1142 patients who used E-TRANS fentanyl had an SAE, 7 of those patients were in the subpopulation of patients with probable renal or hepatic impairment. Overall 13 (4%) of the 361 patients who used IV PCA morphine had an SAE, 1 of those patients was in the subpopulation of patients with probable renal or hepatic impairment.

B. Recommendations

ALZA should determine an opiate conversion scheme for patients who begin use of oral opiates after use of the E-TRANS device.

The sponsor should determine the clinical feasibility of the proposed testing scheme to be done prior to administering the device to a patient. The sponsor should define the logistics of storing and returning defective devices.

Since fentanyl may cause hypoventilation, this product should be used cautiously in patients with conditions that predispose them to hypoventilation e.g. chronic obstructive pulmonary disease. Practitioners should give careful consideration to use of this product in patients with conditions that predispose them to retention of carbon dioxide, e.g. patients with increased intracranial pressure.

Though the sample size is limited, the incidence of adverse events in the subpopulation of patients with renal or hepatic impairment appears higher than in the general population. This should be monitored post-marketing.

Although we do not have a known background rate for comparison, the incidence of embolic events should also be monitored in light of the clinical trial findings.

The intact unused E-TRANS system contains 10 mg of fentanyl. A patient who used all eighty of the allowed 40 mcg doses would have withdrawn 3200 mcg from the system, leaving 6.8 mg residual fentanyl in the hydrogel. In most cases the amount of residual fentanyl in the system would be higher since the clinical studies showed that under 10% of the patients used the maximal allotment of on-demand doses. The risk management plan should

XII. Appendices

A. ASA classifications

ASA I

Patient has no organic, physiologic, biochemical or psychiatric disturbance. The pathological process for which the operation is to be performed is localized and does not entail a systemic disturbance e.g. fibroid uterus in an otherwise healthy woman, or a fit patient with an inguinal hernia.

ASA II

Mild to moderate systemic disturbance caused by either the condition to be treated surgically or by other pathophysiologic processes, e.g. mild diabetes or essential hypertension or anemia.

ASA III

Severe systemic disturbance or disease from whatever cause, even though it may not be possible to define the degree of disability with finality e.g. severe diabetes with vascular complications or angina pectoris or healed myocardial infarction

ASA IV

Indicative of the patient with severe systemic disorders that are already life-threatening, not always correctable by operation e.g. patients with organic heart disease showing marked signs of cardiac insufficiency or advanced degrees of pulmonary, hepatic, renal or endocrine insufficiency

ASA V

The moribund patient who has little chance of survival but is submitted to operation in desperation, e.g. the patients with a burst abdominal aneurysm who is in shock or massive pulmonary embolus.

B. Individual Detailed Study Descriptions

Uncontrolled safety studies

C-93-023

Title:

ETS (fentanyl) pilot efficacy and safety study in the treatment of postoperative pain

Objectives:

- To determine whether a regimen of up to six 25 mcg on-demand doses of fentanyl per hour for 24 hours provided safe and effective management of post-operative pain
- To determine whether a regimen of up to six 40 mcg on-demand doses of fentanyl per hour for 24 hours provided safe and effective management of post-operative pain
- To evaluate the outcome measures to be used in the pivotal efficacy and safety studies.

Population:

Adults who were expected to have moderate to severe postoperative pain

Key inclusion criteria:

- Adults, age 18-75 years, undergoing elective surgery
  - This was changed from persons 18-65 years in amendment 2, dated March 28 1994.
- Moderate to severe pain requiring parenteral opioids for a minimum of 24 hours postoperatively

Key exclusion criteria:

- Treatment with vasoactive agents
- Admission to an intensive care unit
- Another surgical procedure required with 48 hours of surgery
- History of alcohol or substance abuse
- Investigational drug use in the previous 30 days
- Skin disease that would interfere with transdermal fentanyl administration
- Expected to stay in the hospital less than 48 hours
- Receipt of naloxone during surgery or in the immediate postoperative period prior to use of study drug

Study design:

An open-label single-center trial performed in New Zealand.

Study duration:

24 hours of ETS application followed by 24 hours of safety evaluation post-study

Study procedure:
A ETS system was applied for 24 hours to enrolled patients. The patients could self-administer up to 6 doses/hour and receive 25 mcg per dose (Part I) or 40 mcg per dose (Part II). Part II of this study was initiated due to interim analysis demonstrating sub-optimal analgesia with the 25 mcg dose (amendment 4, dated July 13 1994). No patients participated in both parts of the study.

Prior to use of the ETS system, patients had to have been extubated and to have a respiratory rate of 8 breath/minute or greater. They had to have been titrated to analgesia with intravenous fentanyl given as needed. Patients were allowed supplemental titration with single or multiple doses of intravenous fentanyl as rescue medication.

Topical safety was evaluated at 1, 6 and 24 hours after ETS removal.

Blood sampling for pharmacokinetic parameters was done on a subset of patients (Amendment 3, May 24 1994).

Patients were to be terminated from the study if they demonstrated respiratory depression, defined as difficult to arouse with gentle shaking and respiratory rate of under 8 breaths/minute.

A prototype ETS system was used initially but the participants in Part II were given either the prototype or the commercial product for study use (amendment 5, dated March 17 1995).

Outcome measures:
- Pain intensity at rest-VAS (0-100 scale)
- Categorical rating of analgesia by patient
- Number of on-demand fentanyl doses administered
- Global assessments by patient and investigator
- Patient preference questions

Study results:
Description of patients:
Part I:
Seventy-nine patients participated, receiving 25 mcg on-demand dosing of fentanyl. The majority of the participants were female (n=65) and/or Caucasian (n=60). The remainder were described as "Native New Zealander" (n=8) or Asian (n=1). The surgeries included hysterectomy (37 abdominal, 6 vaginal, 2 unspecified), joint replacement (20), laparotomy (11), limb amputation (1), colposuspension (1), bone graft (1).

Part II:
One hundred seventy-four patients participated, receiving 40 mcg on-demand dosing of fentanyl. The majority of the participants were female (n=135) and/or Caucasian (n=99).

The remainder were described as "Native New Zealander" (n=24) or Hispanic (n=1). The surgeries included hysterectomy (61 abdominal, 15 vaginal, 11 unspecified) or other gynecologic surgery (14), joint replacement (48) or other orthopedic surgery (13), laparotomy (4), cholecystectomy (2), hernia repair (2), removal of malignant melanoma (1), lumbar diskectomy (1), abdominal myomectomy (1), revision of colostomy (1).

Sponsor's summary of deaths/discontinuations
There was one death reported from Part I of this study. Patient 125 died 14 days after undergoing a total hip replacement. His recovery was described as uneventful. One week after discharge he returned to the hospital with chest pain and dyspnea. He was thought to have had a pulmonary embolism which led to his death.

While no deaths were reported seven patients discontinued during Part II of this study. Two women discontinued due to internal hemorrhaging and hypotension (231, 335). Two women discontinued due to nausea: one at the patient's request (257), the other at the investigator's request (333). One man was able to complete this study, 93-023, but did not go onto study 94-043 due to marked confusion (341). One man (207)discontinued due to decreased oxygen saturation, hypotension and stupor twenty minutes after an on-demand dose of 40 mcg of fentanyl. He received 0.2 mg of intravenous Narcan and had resolution of his symptoms.

Protocol violations:
One woman was discontinued from Part II when it was discovered that she had received naloxone in the operating room (210).

Pharmacokinetics
Samples (n=899) were obtained from 102 patients: 50 patients in part I; 52 patients in Part II. The mean fentanyl clearance was 35.1 L.

Efficacy
The results from this open-label study were not incorporated into the evaluation of product efficacy.

Safety
Analysis of safety results may be found in Section VII of this review, Integrated Review of Safety.

C-94-043
Title:
ETS pilot efficacy and safety study in the treatment of postoperative pain on Days 2 and 3 Post Surgery

Objective:
To determine whether 6 on-demand doses of 40 mcg fentanyl provided safe and effective management of pain on postoperative days 2 and 3.

Population:
One hundred-fifteen patients who had participated in Part II of study 93-023 were enrolled in this extension study.

Key inclusion criteria:
- Completion of Part II of Study 93-023 (described above)

Key exclusion criteria:
- Patients who were expected to be discharged in under 36 hours
- Patients who had had a significant topical effect from the ETS applied on Day 1

Study design:
An open-label single-center trial performed in New Zealand.

Study duration:
Up to 48 hours per patient

Study conduct:
Patients who had already used an ETS system on postoperative Day 1 were eligible for continued use of the ETS system on postoperative Days 2 and 3.

A new ETS system was applied each day, i.e. on Days 2 and 3 if the patient was willing to participate and had continued need for opioid analgesia.

Patients could self-administer 40 mcg of fentanyl up to six times per hour. Each dose took 10 minutes to be administered.

Outcome measures:
- Pain intensity by visual analog scale
- Patient assessment of quality of analgesia
- Number of on-demand doses of fentanyl administered
- Patient and investigator global assessments

Study results:
Description of patients:
One hundred fifteen patients participated, receiving 40 mcg on-demand dosing of fentanyl. The majority of the participants were female (n=91) and/or Caucasian (n=100). The remainder were described as "Native New Zealander" (n=15). The types of surgeries undergone by this group of patients was summarized previously in the discussion of study 94-023.

Sponsor's summary of deaths/discontinuations
No deaths were reported for this study. Seven patients discontinued this study prior to completion. One patient withdrew for an unspecified reason. Two patients withdrew due

to early discharge from the hospital (1293, 1330). One patient requested discontinuation as she felt that continued analgesia was not necessary (1350). One patient discontinued due to hypertension, and possible left ventricular failure (1362). Two patients withdrew due to inadequate pain relief: one required subcutaneous morphine (1363); one had an increase in pain scores-50 at Hour 4, 35 at hour 8 and 70 at hour 12 (1354).

Protocol violations:
None were reported.

Pharmacokinetics
No pharmacokinetic data was derived from this study.

Efficacy
The results from this open-label study were not incorporated into the evaluation of product efficacy.

Safety
Analysis of safety results may be found in Section VII of this review, Integrated Review of Safety.

C-95-019
Title:
The safety and efficacy of electrotransport (ETS) fentanyl for the management of post-operative pain following short-stay surgical procedures

Objective:
- To evaluate the safety and clinical utility of E-TRANS (40 mcg) for the management of post-operative pain following short stay procedures during the hospitalized post-surgical period and for an additional 24 hours in a medically supervised setting

Population:
A minimum of 75 patients who were scheduled for short-stay surgical procedures

Key inclusion criteria:
- Admission to the post-anesthesia care unit after a short-stay surgical procedure
- Anticipation of discharge from hospital within 24 hours
- Patients for whom oral opioids would normally be prescribed for pain management in the hospital and/or at discharge
- Patients must be awake and breathing spontaneously at a rate of over 8 breaths/minute with a oxygen saturation of 90% or greater (supplemental oxygen is permitted).

Key exclusion criteria:
- Patients with a history of allergy or hypersensitivity to fentanyl
- Patients who are expected to need admission to an intensive care unit

- Patients who have been treated with opioids for chronic pain within two weeks prior to beginning their participation in the study
- Patients with increased intracranial pressure

Study design:
A multi-center open-label single treatment trial

Study duration:
Up to 48 hours per patient
(24 hours in the hospital followed by 24 hours in a medically supervised setting)

Study conduct:
Patients who were determined to be eligible for the study had ETS applied at the beginning of the study, after having been titrated to acceptable analgesia with a parenteral opioid, and ETS replaced after 24 hours.

Pain management using the ETS was provided for the duration of the patient's hospital stay (up to 24 hours) and for up to 24 hours after discharge to a medically supervised setting. Patients kept a diary record of activities engaged in and the number of on-demand fentanyl doses used.

No supplemental analgesic medications were allowed during the study except acetaminophen as needed for fever reduction or headache.

Outcome measures:
- Patient/Investigator global assessment
- Pain intensity-100 mm VAS scale
- Number of on-demand doses delivered
- Topical effects assessments

Study results:
Description of patients:
Seventy-eight patients participated, receiving 40 mcg on-demand dosing of fentanyl. The majority of the participants were female (n=45) and/or Caucasian (n=65). The remainder were described as "Polynesian" (n=13). The surgeries included laparoscopic surgeries (51), orthopedic surgery (16), general surgical procedure (8), breast biopsy (3).

Sponsor's summary of deaths/discontinuations
While no patients were reported to have died while on this study, three patients discontinued this study. Two discontinued due to nausea/vomiting while still in the hospital (127, 166). One participant was discontinued by her physician who felt that the patient needed to remain in the hospital for an additional 24 hours (

Protocol violations:
Patient 141 was hospitalized for 90 minutes longer than specified in the protocol. No other violations were reported.

Pharmacokinetics
No pharmacokinetic data was derived from this study.

Efficacy
The results from this open-label study were not incorporated into the evaluation of product efficacy.

Safety
Analysis of safety results may be found in Section VII of this review, Integrated Review of Safety.

C-96-020
Title:
The efficacy and safety of electrotransport system (ETS) delivery of 25 mcg on-demand doses of fentanyl for the management of postoperative pain following short-stay surgical procedures.

Objective:
- To evaluate the safety and clinical utility of E-TRANS (25 mcg) for the management of post-operative pain following short stay procedures during the hospitalized post-surgical period and for an additional 24 hours in a medically supervised setting

Population:
At least 125 patients to ensure at least 100 evaluable patients

Key inclusion criteria:
- Admission to the post-anesthesia care unit after a short-stay surgical procedure
- Anticipation of discharge from hospital within 24 hours
- Patients for whom oral opioids would normally be prescribed for pain management in the hospital and/or at discharge
- Patients must be awake and breathing spontaneously at a rate of over 8 breaths/minute with a oxygen saturation of 90% or greater (supplemental oxygen is permitted).

Key exclusion criteria:
- Patients with a history of allergy or hypersensitivity to fentanyl
- Patients who are expected to need admission to an intensive care unit
- Patients expected to have post-operative analgesia supplied by a continuous regional technique
- Patients who have been treated with opioids for chronic pain within two weeks prior to beginning their participation in the study

- Patients with increased intracranial pressure

Study design:
A multi-center open-label single treatment trial

Study duration:
24 hours in the hospital and 24 hours in a medically supervised setting after hospital discharge, for a total of up to 48 hours per patient.

Study conduct:
Patients who were determined to be eligible for the study had ETS applied at the beginning of the study, after having been titrated to acceptable analgesia with a parenteral opioid, and ETS replaced after 24 hours.

Pain management using the ETS was provided for the duration of the patient's hospital stay (up to 24 hours) and for up to 24 hours after discharge to a medically supervised setting. Patients kept a diary record of activities engaged in and the number of on-demand fentanyl doses used.

No supplemental analgesic medications were allowed during the study except acetaminophen as needed for fever reduction or headache.

Outcome measures:
- Patient/Investigator global assessment
- Pain intensity-100 mm VAS scale
- Number of on-demand doses delivered
- Topical effects assessments

Study results:
Description of patients:
The study enrolled 102 patients who received 25 mcg on-demand dosing of fentanyl.. Two patients did not complete the study. The majority of the participants were male (n=59) and/or Caucasian (n=86). The remainder were described as "Polynesian" (n=15) or Asian (n=1). The surgeries included laparoscopic surgeries (11), orthopedic surgery (76), general surgical procedure (13), dermatologic procedure (2).

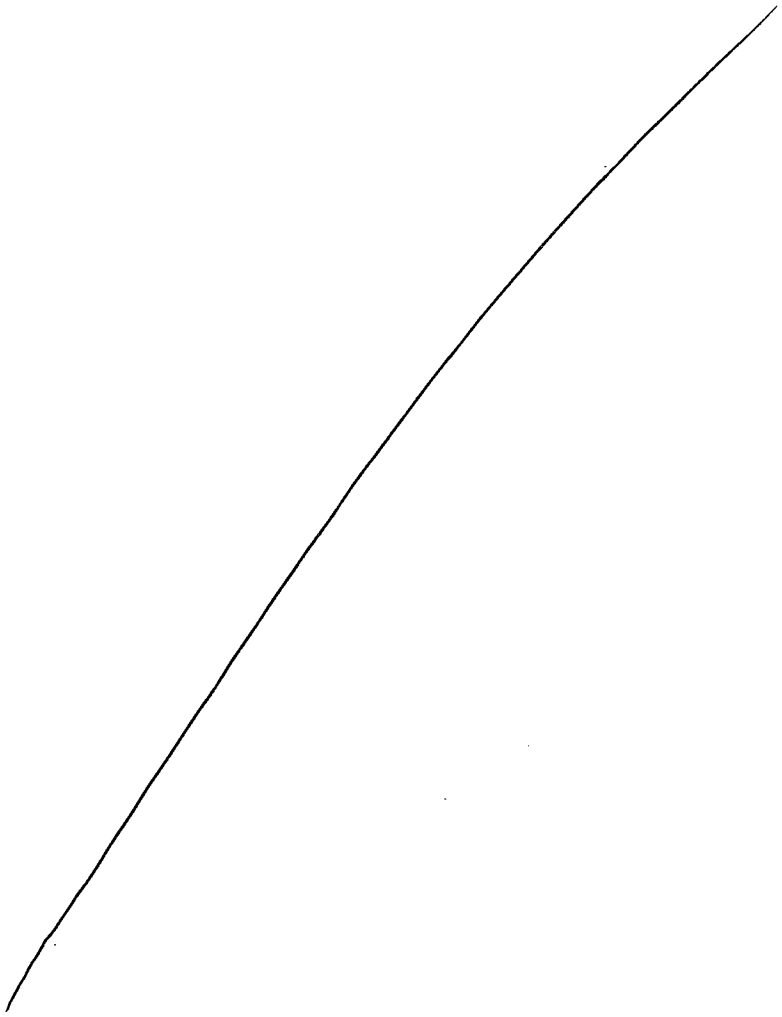
Sponsor's summary of deaths/discontinuations
No deaths were reported from this study. Patient 143 withdrew from the study after 2 hours, having been discharged from the hospital 30 minutes after placement of the E-TRANS system. Patient 162 withdrew from the study upon discharge from the hospital, 30 minutes after E-TRANS placement

Protocol violations:
No violations were reported

Pharmacokinetics
No pharmacokinetic data was derived from this study.

Efficacy
The results from this open-label study were not incorporated into the evaluation of product efficacy.

Safety
Analysis of safety results may be found in Section VII of this review, Integrated Review of Safety.



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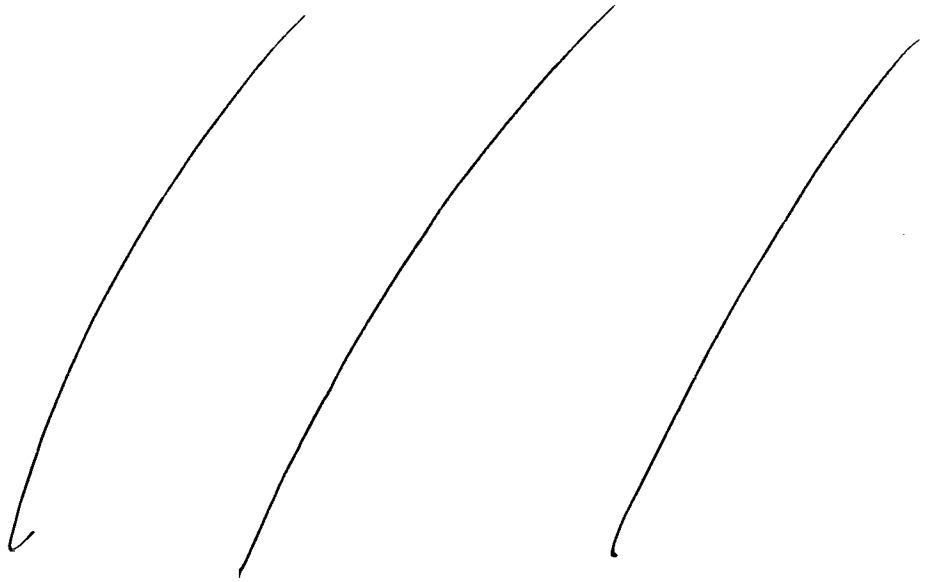
✓ § 552(b)(4) Trade Secret / Confidential

_ § 552(b)(5) Deliberative Process

_ § 552(b)(4) Draft Labeling



C-2000-006

Title:

An open evaluation of safety and clinical utility of E-TRANS (fentanyl) for management of postoperative pain in elderly patients.

Objective:

- To evaluate the safety and clinical utility of E-Trans (fentanyl) System-25 mcg for pain management in elderly postoperative patients.

Population:

Up to 95 elderly inpatients aged 65 or older who were expected to require opioid analgesia for moderate to severe pain

Key inclusion criteria:

- Age 65 years or older
- ASA status I, II or III
- Admission to the post-anesthesia care unit after major abdominal, orthopedic or thoracic surgery
- Patients who are expected to remain hospitalized and to have pain requiring parenteral opioids for the next 24 hours or longer
- Patients must be awake and breathing spontaneously at 8-24 breaths/minute with a oxygen saturation of 90% or greater (supplemental oxygen is permitted)

- Patients who have been in the PACU at least 30 minutes and are comfortable or have been titrated to comfort with IV opioids

Key exclusion criteria:

- Patients with a history of allergy or hypersensitivity to fentanyl
- Patients who are expected to need admission to an intensive care unit
- Patients who received a long-lasting intra-operative regional analgesic or who were expected to have post-operative analgesia supplied by a continuous regional technique
- Patients with active skin disease
- Patients who have been treated with opioids for chronic pain within two weeks prior to beginning their participation in the study or who had a history of opioid dependence
- Patients who receive intra-operative and/or post-operative administration of opioids other than morphine, fentanyl, sufentanil or alfentanil. A single dose of meperidine was allowed for treatment of shivering if given within 30 minutes of arriving in the PACU.
- Patients with increased intracranial pressure
- Patients who are intubated at the time of final screening assessments

Study design:
A multicenter, open-label, single-treatment study in the Unites States of America

Study duration:
Up to 72 hours per patient

Study procedure:
Once the patient had been in the PACU for at least 30 minutes they were to be assessed for pain intensity, vital signs and oxygen saturation. If needed, patients were to be titrated to comfort as they recovered from anesthesia. If the patient was found to be eligible for study, pain intensity, oxygen saturation and vital signs were to be assessed again to begin the treatment period (Hour 0).

All patients were to receive 25 mcg on-demand dosing via E-TRANS. The patients would then wear E-TRANS for up to 72 hours. Patients were allowed to receive IV fentanyl as rescue medication in the first three hours of study participation. Only the patient or the investigator's staff was allowed to activate the E-TRANS system. Family members were not allowed to do so.

At each 24 hour assessment period, global assessments were done by the patient and the investigator. It the patient withdrew from the study prior to the scheduled 24 hour assessment, the pain intensity and global assessments were completed at the time of withdrawal.

Outcome measures:

- Pain intensity (VAS)
- Patient global assessments
- Investigator global assessments
- Assessment of adherence of the E-TRANS system
- Vital signs including oxygen saturation

Study results:

Description of patients:

This study screened 119 patients and enrolled 95 patients. The majority of the patients were between 65 and 74 years old (n=62), with the remained being 75 years or above. The enrolled subjects were predominantly female (n=65, 68.4%) and Caucasian (n=91, 95.8%). The majority of the surgeries were orthopedic (n=48, 50.5%), with the remainder being abdominal (lower 41%, upper 2%), thoracic (3%) or other (3%).

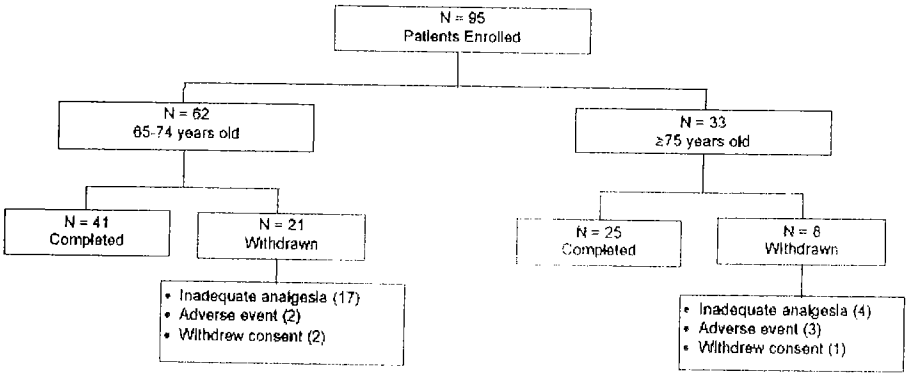
Sponsor's summary of deaths/discontinuations:

The sponsor reported one death, patient 110. This woman underwent an exploratory laparotomy for serous adenocarcinoma metastatic throughout the peritoneum on . She received E-TRANS fentanyl for postoperative analgesia. She completed 24 hours on study. On , she was noted to have a pleural effusion and possible small bowel obstruction. A VQ scan was thought to be consistent with a pulmonary embolism. She died on . The recorded causes of death were cardiac arrest, ovarian cancer and peritoneal cancer.

Twenty nine of the 95 enrolled patients withdrew from the study prior to completion. The majority of these patients withdrew due to inadequate analgesia (n=21:105,106,107, 207, 208, 304, 306, 402, 404, 407, 609, 826, 828, 829, 837, 901, 903, 908, 3103, 3104, 3106). Five patients withdrew due to adverse events (206,605,604 610,819) and three withdrew consent (305,611,827).

Reviewer's note: At the time of withdrawal of consent patient 827 rated pain as 99/100 and global assessment of E-TRANS efficacy was poor. Her withdrawal should have been counted as inadequate analgesia.

Table: Patient disposition (from study report C-2000-006)



Source: Table 11.2.2.1-1

Protocol violations:
While most of the deviations reported by ALZA represented assessments that were not conducted according to schedule, there were other more serious violations.

Patient 803's family was administering the on-demand dosing instead of the patient. The patient was estimated to have received 113 doses of fentanyl, using two distinct E-TRANS systems. Somnolence was reported as a SAE 8 hours after the patient was terminated from the study. While the SAE was considered treatment related, the blood samples which were to be drawn in the case of any SAE were not obtained.

Four patients received medication that was not permitted according to protocol: morphine (patient 107), meperidine (patient 605), opioids (patient 610), vioxx (patient 613).

Pharmacokinetics
No pharmacokinetic data was derived from this study.

Efficacy
The results from this open-label study were not incorporated into the evaluation of product efficacy.

Safety
Analysis of safety results may be found in Section VII of this review, Integrated Review of Safety.

C-2000-009
Title:
An open evaluation of the safety and clinical utility of E-TRANS for the management of post-operative pain following short-stay procedures

Objective:
- To evaluate the safety and clinical utility of E-TRANS (25 mcg) for the management of post-operative pain following short stay procedures during the hospitalized post-surgical period and for an additional 24 hours in a medically supervised setting

Population:
Up to 375 patients to ensure at least 300 evaluable patients

Key inclusion criteria:
- Adults of either gender
- Pre- and post- operative ASA physical status I, II or III
- Admission to the post-anesthesia care unit after a short-stay surgical procedure, an orthopedic procedure, a hernia repair, or a proctological procedure
- Anticipation of discharge from hospital within 24 hours
- Patients for whom oral opioids would normally be prescribed for pain management in the hospital and/or at discharge

- Patients must be awake and breathing spontaneously at a rate of 8-24 breaths/minute with a oxygen saturation of 90% or greater (supplemental oxygen is permitted).
- Patients must have been in the PACU for at least 30 minutes and must be comfortable or have been titrated to comfort with IV opioids

Key exclusion criteria:

- Patients with a history of allergy or hypersensitivity to fentanyl
- Patients who are expected to need admission to an intensive care unit
- Patients who received a long-lasting intra-operative regional analgesic or who are expected to have post-operative analgesia supplied by a continuous regional technique
- Patients who have been treated with opioids for chronic pain within two weeks prior to beginning their participation in the study
- Patients with increased intracranial pressure
- Patients who are expected to need additional surgical procedures within 36 hours
- Patients who receive intra-operative and/or post-operative administration of opioids other than morphine, fentanyl, sufentanil or alfentanil. A single dose of meperidine was allowed for treatment of shivering if given within 30 minutes of arriving in the PACU.
- Patients who are intubated at the time of final screening assessments
- Patients who are suspected of being or who are known to be opioid tolerant
- Patients with active skin disease

Study design:
A multi-center open-label single treatment trial

Study duration:
24 hours in the hospital and 24 hours in a medically supervised setting (MSS) after hospital discharge, for a total of up to 48 hours per patient.

Study conduct:
Patients who were determined to be eligible for the study had ETS applied at the beginning of the study, after having been titrated to acceptable analgesia with a parenteral opioid, and ETS replaced after 24 hours.

Pain management using the ETS was provided for the duration of the patient's hospital stay (up to 24 hours) and for up to 24 hours after discharge to a medically supervised setting. Patients kept a diary record of activities engaged in and the number of on-demand fentanyl doses used.

No supplemental analgesic medications were allowed during the study except acetaminophen as needed for fever reduction or headache.

Outcome measures:

- Patient/Investigator global assessment
- Pain intensity-100 mm VAS scale
- Topical effects assessments
- Adverse events

Study results:

Description of patients:

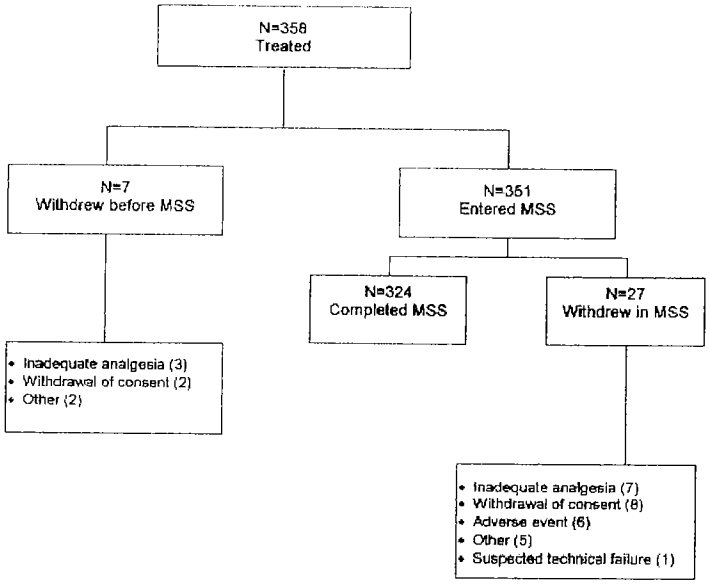
The study enrolled 358 patients who received 25 mcg on-demand dosing of fentanyl. The majority of them (n=358) continued past 24 hours and used E-TRANS in an outpatient medically supervised setting. All but two of these patients wore the system both in the hospital and in the medically supervised setting. Two patients were discharged directly from the PACU to the medically supervised setting.

The majority of the 358 participants were female (n=227) and/or Caucasian (n=301). The remainder were described as Black (n=29), Hispanic (n=20) or Other (n=1). The surgeries included orthopedic surgery (196), thoracic/chest surgery (39), abdominal surgery (upper n=27, lower n=32), neurological procedures (8) and other (49).

Sponsor's summary of deaths/discontinuations

No deaths were reported from this study.

Thirty-four of the 358 enrolled patients withdrew from the study prior to completion. The majority of these patients withdrew due to inadequate analgesia (n=10: 108, 241, 321, 436, 524,1019,1047,1069,1308,1324). Six patients withdrew due to adverse events (430, 517, 532,1015,1314, 1333) and seven withdrew consent (501, 512, 529, 601, 602, 603, 1353). Seven withdrew for other reasons (314, 315, 317, 320, 1055, 1102, 1119, 1326, 2304, 3026). One withdrew due to suspected technical failure (1326).



Source: Table 11.2.2-1

Protocol violations:
Nine patients had non-surgical neurologic procedures performed. There were multiple instances where the number of demand doses reported did not correlate with the number of flashes seen.

Pharmacokinetics
No pharmacokinetic data was derived from this study.

Efficacy
The results from this open-label study were not incorporated into the evaluation of product efficacy.

Safety
Analysis of safety results may be found in Section VII of this review, Integrated Review of Safety.

Wearing studies using placebo E-TRANS systems
C-95-034
Title:
Wearing study for non-drug containing ETS systems comprised of selected aspects of the ETS (fentanyl) Commercial System Design.

Objectives:
- To identify the optimal configurations for selected aspects of the circuitry. [redacted] and the skin adhesive that will be included in the E-TRANS (fentanyl HCL) System commercial system design
- To identify the recommended body sites for application.

Population:
24 healthy volunteers

Key inclusion criteria:
- Healthy adults ages 18 to 65 years

Key exclusion criteria:
- Active skin disease at the application site
- History of skin allergies or adhesive sensitivity
- Sensitivity to any component of the delivery system

Study design:
A single center, randomized open-label two-phase study.

Study duration:
24.33 hours

Study conduct:

Phase I

Three identical systems were worn simultaneously for up to 20 minutes: one on the upper outer arm, one on the lower inner opposite arm and one on the upper chest.

This phase was designed to investigate the time needed to achieve an output current density of 76 $\mu A/cm^2$ and in the time-to-compliance function relating output current density achieved to time after ETS activation. Voltage was applied for up to 20 minutes . The parameters of interest were compared across the three sites. The results were used to determine the recommended application sites for the use of E-TRANS in patients.

Phase II

This phase was designed to investigate the operational functionality of a circuitry modification and of [redacted] for use with the modified circuit. These parameters were compared with the systems used in protocol C95-003. The effectiveness of two different adhesive configurations was also evaluated.

Outcome measures:

Adverse events, specifically topical effects at the anode, cathode and adhesive sites were assessed for 24 hours after removal of the systems.

Study results:

Description of subjects:

There were 12 persons of each gender in this study. Twelve Caucasians participated . Nine subjects were between 18 and 30 years old. Nine were between 31 and 50 years old. The remainder were between 51 and 65 years old.

Sponsor's summary of deaths/discontinuations

None reported.

Protocol violations:

None reported.

Pharmacokinetics

No medications were used in this study.

Efficacy

Efficacy was not assessed in this study.

As a result of these studies, ALZA determined that application on the chest provided the best time to compliance. Th[redacted] adhesive thicknesses were suboptimal. The interface configurations tested ([redacted] and [redacted] were both appropriate for further study.

Safety

The participants in this study did not receive any fentanyl. The adverse events that were experienced could all be related to the patch application. Minimal erythema was noted at five sites and papules were noted at one site within 60 minutes of patch removal. One subject noted a burning sensation which resolved within 10 minutes. Another subject developed papules, and pruritis with evidence of irritation at one site. These symptoms resolved after use of 25 milligrams of diphenhydramine.

C-95-050

Title:

Evaluation of the effect of alcohol pretreatment of the skin on the time to achieve compliance using non-drug containing ETS systems comprised of selected aspects of the ETS Commercial System design

Objective:

- To evaluate the effect of alcohol pretreatment of the skin on the time required to achieve an output current density of 76 $\mu A/cm^2$.

Population:

24 healthy volunteers, with equal distribution across genders

Key inclusion criteria:

Healthy adults between age 18 and 65 years

Key exclusion criteria:

- Active skin disease at the application site
- History of skin allergies or adhesive sensitivity
- Sensitivity to any component of the delivery system

Study design:

Single center open-label randomized study

Study duration:

Twenty minutes of electrical current administration with follow-up after 24 hours.

Study conduct:

Volunteers were to be randomly assigned to Group I: pretreatment with alcohol or Group II: No pretreatment before application of the first E-TRANS system. During use of the second system, the participant was to be assigned to the other group.

An E-TRANS system was to be applied to the right upper outer arm and secured with tape. The system was to be activated to produce a 10-minute current. Anode and cathode voltages were to be measured.

Fifteen minutes later, an E-TRANS system was to be applied to the left upper outer arm and secured with tape. The system was to be activated to produce a 10-minute current. Anode and cathode voltages were to be measured.

Fifteen minutes later, an E-TRANS system on the right upper outer arm to be re-activated to produce a 10-minute current. Anode and cathode voltages were to be measured.

Fifteen minutes after that, an E-TRANS system on the left upper outer arm was to be re-activated to produce a 10-minute current. Anode and cathode voltages were to be measured.

Participants were to be allowed to leave after both systems had been tested twice and removed.

Outcome measures:
The time to compliance was the primary endpoint.
Adverse reactions were also assessed.

Study results:
Description of subjects:
There were 12 persons of each gender in this study. Thirteen Caucasians participated . Seven subjects were between 18 and 30 years old. Nine were between 31 and 50 years old. The remainder were between 51 and 65 years old.

Sponsor's summary of deaths/discontinuations
None reported.

Protocol violations:
None reported.

Pharmacokinetics
No medications were used in this study.

Efficacy
Efficacy was not assessed in this study.

Sites which had not been pretreated (12.1 seconds with a SD of 16) were found to have a longer time to compliance with more variability than systems applied to sites which had been pretreated with alcohol (4.3 seconds with a SD of 3.1 seconds).

Safety
The participants in this study did not receive any fentanyl. There were no systemic adverse effects nor topical effect noted 24 hours after system removal.

C-95-051

Title:
Evaluation of skin adhesives for the E-TRANS system

Objective:
- To identify the optimal adhesive for the E-TRANS system. Four adhesives were compared.

Population:
24 healthy volunteers, with equal distribution across genders

Key inclusion criteria:
- Healthy adults between age 18 and 65 years

Key exclusion criteria:
- Active skin disease at the application site
- History of skin allergies or adhesive sensitivity
- Sensitivity to any component of the delivery system

Study design:
Single center open-label randomized study

Study duration:
2 weeks

Study conduct:
Four E-TRANS systems, each with different adhesives, were tested for a 72-hour wearing period. Two were applied to the upper chest and two were applied to the upper outer arm.

Outcome measures:
- Adhesive performance was evaluated: percentage adhesion; end-lift and side-lift of systems: assessment of wearing comfort; difficulty of removal; discomfort on removal.
- Systemic and topical adverse events throughout the study. Topical adverse events were also assessed at 0, 1, 6 and 24 hours after system removal.

Study results:
Description of patients:
None given.

Sponsor's summary of deaths/discontinuations
Twenty-five people were enrolled. All but one completed the trial. No explanation was given for the discontinuation

Protocol violations:
None reported.

Pharmacokinetics
No drug was used in this study.

Efficacy
Drug efficacy was not evaluated during this study.
The [redacted] adhesive formulations were the best when the adhesion parameters were reviewed. It was noted that the results from this study might not be directly applicable to the commercial product since the bottom housing used in this study was different than the proposed commercial form.

Safety
The participants in this study did not receive any fentanyl.

The adverse events experienced were related to the patch application. Erythema was noted at 10% of [redacted] sites and 27% of [redacted] sites.

C-95-053
Title:
Evaluation of skin adhesives for the ETS (fentanyl) Commercial System Design

Objective:
- To identify the optimal adhesive for the E-TRANS system

Population:
24 healthy volunteers, with equal distribution across genders

Key inclusion criteria:
- Healthy adults between age 18 and 65 years

Key exclusion criteria:
- Active skin disease at the application site
- History of skin allergies or adhesive sensitivity
- Sensitivity to any component of the delivery system

Study design:
A single-center open-label study.

Study duration:
24 hours

Study conduct:
Two E-TRANS systems were applied to each arm, for a total of four systems. worn/patient. Each system had a different adhesive formulation.

Outcome measures:
The primary measurement was system adhesion, though secondary measurements included end-lift, side lift, assessment of difficulty of ETS system removal, topical effects following ETS removal and other adverse events.

Study results:
Description of patients:
None given.

Sponsor's summary of deaths/discontinuations:
Twenty-four subjects were enrolled and completed the study but the CRFs for one subject were lost.

Protocol violations:
None reported.

Pharmacokinetics
No drug was used in this study.

Efficacy
Drug efficacy was not evaluated during this study. The MA-24 adhesive formulation performed the best.

Safety
The participants in this study did not receive any fentanyl.

Erythema, described as barely perceptible, was noted and resolved within 24 hours in all but one subject. Mild itching was also described.

C-96-003
Title:
Wearing study of an E-TRANS system in elderly and younger adult subjects

Objective:
- To assess the discomfort and difficulty of removing E-TRANS systems after 24 hours wear by elderly subjects
- To assess difficulty of removing E-TRANS systems after 24 hours wear by young subjects

Population:
Up to 112 subjects with 52 subjects between the ages of 18 to 45 years and 52 subjects between the ages of 65 to 80 years old.

Key inclusion criteria:
- Healthy adults between age 18 and 45 years (inclusive), or between 65 to 80 years (inclusive)

Key exclusion criteria:
- Active skin disease at the application site
- History of skin allergies or adhesive sensitivity
- Sensitivity to any component of the delivery system

Study design:
A single-center, open-label, single treatment study.

Study duration:
24 hours

Study conduct:
One E-TRANS system was worn on an outer upper arm of each subject for 24 hours.

Outcome measures:
The primary measurement was an assessment of the difficulty of E-TRANS system removal. The secondary measurements include system adhesion, qualititative evaluation of wearing comfort, assessment of the discomfort of system removal.

Study results:
Description of patients:
Fifty two subjects between age 18 and 45 years (inclusive) were enrolled and 51 subjects between 65 to 80 years (inclusive).

Sponsor's summary of deaths/discontinuations:
One subject in the younger age group discontinued due to dental pain.

Protocol violations:
None reported.

Pharmacokinetics
No drug was used in this study.

Efficacy
Drug efficacy was not evaluated during this study.

While all subjects reported no or minimal discomfort while wearing the E-TRANS system, 90% of young subjects reported no or minimal difficulty with removal while 14% of elderly subjects reported removal was moderately or very difficult. All of the young subjects reported no or minimal discomfort after system removal, 82% of the elderly subjects reported that level of discomfort.

Nine subjects (one young, eight elderly) had systems fall off during the trial. The poor adhesion was attributed to the age of a component of the adhesive. Manufacturing specifications were changed to specify the maximum age of the components of the adhesive.

Safety
The participants in this study did not receive any fentanyl.

Younger subjects noted erythema (94%), edema (17%) and papules (31%) shortly after removal of the system. These symptoms resolved in all but one subject within 24 hours of system removal.

Elderly subjects also noted erythema (61%), edema (8%) and papules (14%) shortly after removal of the system. One elderly subject noted pustules at the site. These symptoms resolved in all but one subject within 24 hours of system removal.

A total of six patients reported pruritis. One patient reported dental pain which led to study discontinuation and another reported a headache, otherwise no non-dermatological effects were reported.

Additional studies :
FEN-INT-006
Title:
Investigation of the postoperative analgesic effects of three demand dose sizes of fentanyl administered by PCA

Objective:
To assess the optimal dose of fentanyl for use in patient-controlled analgesia in patients with moderate to severe postoperative pain associated with major abdominal surgery.

Population:
150 patients with moderate to severe postoperative pain associated with major abdominal surgery

Key inclusion criteria:
- Patients, 21-75 years old who had had major abdominal surgery
- Moderate to severe pain requiring parenteral opioids for a minimum of 24 hours postoperatively
- Oxygen saturation of 90% or greater

- Titrated to acceptable analgesia (VAS less than or equal to 2)

Key exclusion criteria:

- Procedures requiring postoperative sedation, ventilatory support, treatment with vasoactive agents or ICU admission
- Need for another surgical procedure within 36 hours of the end of surgery
- Opioid treatment for chronic pain within 3 days before surgery
- History of substance abuse

Study design:
A multi-center, randomized, double-blind, parallel group dose-ranging study

Study duration:
24 hours

Study conduct:
This study was amended twice prior to initiation of patient enrollment. The first amendment altered the procedures for management of respiratory depression and the second amendment increased the study doses from 12.5 mcg, 25 mcg and 50 mcg to 20 mcg, 40 mcg and 60 mcg.

Patients with moderate to severe pain (VAS >5, on a 0-10 scale) were titrated with fentanyl postoperatively until they had a decrease in VAS score to 2 or less. At that time the patient was given a patient controlled analgesic (PCA) device which would provide a fixed dose of fentanyl up to 6 times/hour. The study participants were randomly assigned to receive either 20 mcg, 40 mcg or 60 mcg on-demand (50 participants/dose level).

Outcome measures:
The primary efficacy parameter was the number of responders defined as a global assessment score of very good /excellent and no severe opioid adverse effects.

The secondary efficacy parameters were pain intensity at rest and during movement, number of fentanyl demand doses requested, global assessment scores.

Safety was assessed by monitoring of adverse events, pulse oximetry and vital signs.

Study results:
Description of patients:
Fifty patients were enrolled in each group. The enrolled patients, 146 of whom were White, included 76 female patients and 74 male patients.

Sponsor's summary of deaths/discontinuations
Seven patients discontinued the study. One (60 mcg group) discontinued due to an adverse experience: respiratory depression. One (40 mcg group) withdrew since "out of

trial medicine". The other five withdrew due to insufficient analgesia: 2 in the 20 mcg group, 2 in the 40 mcg group and 1 in the 60 mcg group.

Protocol violations:
None reported

Pharmacokinetics
One of the study sites obtained blood samples (n=31/150) for determination of fentanyl concentration. Pharmacokinetic results have been discussed in Section III, Pharmacokinetics and Pharmacodynamics.

Efficacy
The results from this dose-ranging study were not incorporated into the evaluation of product efficacy.

Safety
Analysis of safety results may be found in Section VII of this review, Integrated Review of Safety.

Studies which were stopped prematurely due to technical problems with the E-TRANS system

C-94-057

Title:
The safety and efficacy of Electrotransport (E-TRANS) fentanyl compared to IV PCA morphine for treatment of postoperative pain.

Objective:
Compare the safety, efficacy and patient satisfaction of E-TRANS fentanyl 40 mcg to IV PCA morphine for the management of post-operative pain in adult patients

Population:
Up to 630 adult patients admitted to the post-anesthesia care unit who were expected to have moderate to severe pain requiring parenteral opioids for at least 24 hours post-operatively

Key inclusion criteria:

- Patients aged ≥18 years of either gender
- At the time of initiation of post-operative analgesic management, patient must be of a clinical condition that would normally be considered suitable for IV PCA therapy at a participating study center
- Patients admitted to the post-anesthesia care unit after surgery, who are expected to have moderate to severe pain requiring parenteral opioids for at least 24 hours after their surgery
- Patients awake and breathing spontaneously with oxygen saturation of 90% or greater and the ability to answer questions and follow commands

- Patients who have been titrated to comfort for at least 30 minutes

Key exclusion criteria:

- Expectation of postoperative analgesia supplied by a continuous regional technique
- Expectation of need for intensive care
- Requirement for another surgical procedure within 36 hours of the first procedure
- Use of intra-operative and/or post-operative administration of opioids other than morphine, fentanyl, sufentanil or alfentanil
- Known or suspected opioid tolerance
- History of opioid dependence

Study design:
An open-label, multi-center, randomized, active-controlled, parallel-group trial.

Study duration:
Up to 72 hours

Study conduct:
After recovery from intraoperative analgesia, patients were titrated to comfort using intravenous morphine, fentanyl, sufentanil or alfentanil. Patients who were eligible for study entry were then randomized to receive either a E-TRANS system or IV morphine. Patients used their assigned form of analgesia for 24 hours. After the initial 24 hours, patients were given the option to continue use of the assigned therapy for up to two more 24 hour periods. During the study patients were assessed for pain intensity, number of on-demand doses delivered, oxygen saturation and vital signs. Global assessments were performed at 24, 48 and 72 hours on study.

Outcome measures:
The planned primary efficacy measurement was the patient global assessment score at the 24 hour time point. The planned safety outcome measures were adverse events, respiratory function, vital signs, oxygen saturation and assessment of topical adverse events.

Study results:
Description of patients:
Eighty-three patients were enrolled before the study was discontinued due to E-TRANS system technical failures. ALZA reports that [redacted] led to premature system shutdown after an undetermined period of use.

Forty-two patients were enrolled in the E-TRANS fentanyl group and forty-one were enrolled in the IV PCA morphine group. The enrolled patients, 63 of whom were White, included 77 female patients and 6 male patients. The surgeries included orthopedic surgery (n=8), lower abdominal surgery (n=68), thoracic/chest (n=2), upper abdominal surgery (n=2) and others (n=3).

Seventeen patients used one E-TRANS system. Twelve patients used two E-TRANS systems. Nine patients applied three E-TRANS systems. Four patients applied 4 E-TRANS systems. Fifty-six patients were considered to have completed the study: 7 patients completed 72 hours; 49 patients had no further need for analgesia.

Sponsor's summary of deaths/discontinuations
No deaths were reported during this study.

Five people withdrew due to unrelieved post-operative pain: 4 in the E-TRANS group (30008, 30102, 30224, 30267) and 1 in the IV PCA morphine group (30272). Three people discontinued due to an adverse event: 2 in the E-TRANS group (30404,30405): 1 in the IV PCA morphine group (30039). Three people were discontinued due to non-compliance:1 in the E-TRANS fentanyl group (30036); 2 in the IV PCA morphine group (30023, 30185). Sixteen patients discontinued for other reasons: 5 (30101, 30104, 30183, 30265, 30270) in the E-TRANS fentanyl group; 11 in the IV PCA morphine group (30081,30105, 30106, 30109, 30188, 30189, 30190,30264,30266,30271, 30406).

Protocol violations:
One patient, who was withdrawn from the study, had not been titrated to comfort before entering the study.

Pharmacokinetics
No pharmacokinetic results were obtained from this study.

Efficacy
The sponsor did not perform an efficacy analysis since the time of system breakdown was unknown.

Safety
Analysis of safety results may be found in Section VII of this review, Integrated Review of Safety.

C-94-058
Title:
The safety and efficacy of Electrotransport (E-TRANS) fentanyl compared to IM morphine for treatment of postoperative pain.

Objective:
Compare the safety and efficacy of E-TRANS fentanyl 40 mcg to IM morphine for the management of post-operative pain in adult patients

Population:
Up to 630 adult patients admitted to the post-anesthesia care unit who were expected to have moderate to severe pain requiring parenteral opioids for at least 24 hours post-operatively

Key inclusion criteria:

- Patients aged ≥18 years of either gender
- At the time of initiation of post-operative analgesic management, patient must be of a clinical condition that would normally be considered suitable for IV PCA therapy at a participating study center
- Patients admitted to the post-anesthesia care unit after surgery, who are expected to have moderate to severe pain requiring parenteral opioids for at least 24 hours after their surgery
- Patients awake and breathing spontaneously with oxygen saturation of 90% or greater and the ability to answer questions and follow commands
- Patients who have been titrated to comfort for at least 30 minutes

Key exclusion criteria:

- Expectation of postoperative analgesia supplied by a continuous regional technique
- Expectation of need for intensive care
- Requirement for another surgical procedure within 36 hours of the first procedure
- Use of intra-operative and/or post-operative administration of opioids other than morphine, fentanyl, sufentanil or alfentanil
- Known or suspected opioid tolerance
- History of opioid dependence

Study design:
An open-label, multi-center, randomized, active-controlled, parallel-group trial performed in the Netherlands, Canada, Denmark, Austria and Belgium and the United Kingdom.

Study duration:
Up to 72 hours

Study conduct:
After recovery from intraoperative analgesia, patients were titrated to comfort using intravenous morphine, fentanyl, sufentanil or alfentanil. Patients who were eligible for study entry were then randomized to receive either a E-TRANS system or IM morphine. Patients used their assigned form of analgesia for 24 hours. After the initial 24 hours, patients were given the option to continue use of the assigned therapy for up to two more 24 hour periods. During the study patients were assessed for pain intensity, number of on-demand doses delivered, oxygen saturation and vital signs. Global assessments were performed at 24, 48 and 72 hours on study.

Outcome measures:
The planned primary efficacy measurement was the patient global assessment score at the 24 hour time point. The planned safety outcome measures were adverse events,

respiratory function, vital signs, oxygen saturation and assessment of topical adverse events.

Study results:

Description of patients:

Eighty-five patients were enrolled before the study was discontinued due to E-TRANS system technical failures. ALZA reports that [redacted] led to premature system shutdown after an undetermined period of use.

Forty-one patients were enrolled in the E-TRANS fentanyl group and forty-four were enrolled in the IM morphine group. One patient who had been randomized to IM morphine was never treated. The enrolled patients included forty-eight female patients and thirty-six male patients, eighty-two of whom were White. The surgeries included orthopedic surgery (n=37), lower abdominal surgery (n=32, thoracic/chest (n=10), upper abdominal surgery (n=2) and others (n=3).

Sixteen patients used one E-TRANS system. Twelve patients used two E-TRANS systems. Eleven patients applied three E-TRANS systems. Two patients applied 4 E-TRANS systems. Sixty-four patients were considered to have completed the study: 20 patients completed 72 hours; 44 patients had no further need for analgesia.

Sponsor's summary of deaths/discontinuations

No deaths were reported during this study. Two patients, both of whom received E-TRANS fentanyl, died after the study: patient 30235 died within 30 days of study completion; patient 30598 died 5 weeks after completing the study.

Eight people withdrew due to unrelieved post-operative pain: 6 in the E-TRANS group (30005, 30139, 30371, 30421, 30432, 30445) and 2 in the IM morphine group (30415,30422). Seven persons discontinued due to an adverse event: 4 in the E-TRANS group (30046, 30220, 30431, 30598): 3 in the IM morphine group (30050, 30228, 30320). Three people were discontinued due to non-compliance:2 in the E-TRANS fentanyl group (30045, 30135); 1 in the IM morphine group (30097). Two patients in the E-TRANS fentanyl group discontinued for other reasons i.e. technical failure, nausea/fear (30425, 30703).

Protocol violations:

No protocol violations were reported.

Pharmacokinetics

No pharmacokinetic results were obtained from this study.

Efficacy

The sponsor did not perform an efficacy analysis since the time of system breakdown was unknown.

Safety
Analysis of safety results may be found in Section VII of this review, Integrated Review of Safety.

C-94-059
Title:
The safety and efficacy of Electrotransport (E-TRANS) fentanyl for treatment of postoperative pain: a double-blind multi-center placebo-controlled trial.

Objective:
Compare the safety and efficacy of E-TRANS fentanyl 40 mcg, with E-TRANS placebo for the management of post-operative pain in adult patients

Population:
Up to 184 adult patients admitted to the post-anesthesia care unit who were expected to remain hospitalized and require parenteral opioids for at least 24 hours post-operatively

Key inclusion criteria:
- Patients aged ≥18 years of either gender
- At the time of initiation of post-operative analgesic management, patient must be of a clinical condition that would normally be considered suitable for IV PCA therapy at a participating study center
- Patients admitted to the post-anesthesia care unit after surgery, who are expected to remain hospitalized and to have moderate to severe pain requiring parenteral opioids for at least 24 hours after their surgery
- Patients awake and breathing spontaneously with oxygen saturation of 90% or greater and the ability to answer questions and follow commands
- Patients who have been titrated to comfort for at least 30 minutes

Key exclusion criteria:
- Expectation of postoperative analgesia supplied by a continuous regional technique
- Expectation of need for intensive care
- Requirement for another surgical procedure within 36 hours of the first procedure
- Use of intra-operative and/or post-operative administration of opioids other than morphine, fentanyl, sufentanil or alfentanil
- Known or suspected opioid tolerance
- History of opioid dependence

Study design:
A double-blind multi-center, randomized placebo-controlled, parallel-group trial performed in Sweden, Norway, South Africa and the United Kingdom.

Study duration:
Up to 24 hours of E-TRANS use

Study conduct:
After recovery from intraoperative analgesia, patients were titrated to comfort using intravenous morphine, fentanyl, sufentanil or alfentanil. Patients who were eligible for study entry were then randomized to receive either a E-TRANS system or a E-TRANS placebo system. The protocol specified that rescue medication was available during the first three hours after patch placement as needed for re-titration to comfort.

During the study period of up to 24 hours, patients were assessed for level of pain intensity, number of on-demand doses required, oxygen saturation and vital signs.

Outcome measures:
The planned safety outcome measures were adverse events, respiratory function, vital signs, oxygen saturation and assessment of site reactions.

Study results:
Description of patients:
Twenty-one patients were enrolled before the study was discontinued due to E-TRANS system technical failures. ALZA reports that battery and/or switch corrosion led to premature system shutdown after an undetermined period of use.

Sixteen patients were enrolled in the E-TRANS fentanyl group and five were enrolled in the E-TRANS placebo group. The enrolled patients included eight female patients and eight male patients, nineteen of whom were White. The surgeries included orthopedic surgery (n=3), lower abdominal surgery (n=13) thoracic/chest (n=1), upper abdominal surgery (n=2) and others (n=2).

Twenty-one patients used two E-TRANS systems. Six patients applied three E-TRANS systems. Twelve patients were considered to have completed the study: nine completed 24 hours; one received the maximum of 80 doses but was noted to have inadequate analgesia (30226).

Sponsor's summary of deaths/discontinuations
No deaths were reported. Four people (30140, 30223, 30225, 30226) withdrew due to post-operative pain unrelieved by the E-TRANS system: 2 in each group. One person in the E-TRANS fentanyl group (30135) was discontinued due to non-compliance. One person in the placebo group discontinued due to an adverse event (30136). Three in the E-TRANS fentanyl group discontinued for other reasons i.e. technical failure (30060, 30082, 30133).

Protocol violations:
No protocol violations were reported.

Pharmacokinetics
No pharmacokinetic results were obtained from this study.

Efficacy
The sponsor did not perform an efficacy analysis since the time of system breakdown was unknown for all patients.

Safety
Analysis of safety results may be found in Section VII of this review, Integrated Review of Safety.

C-96-055
Title:
An open evaluation of safety and efficacy of E-TRANS (fentanyl) for management of postoperative pain following short-stay surgical procedures.

Objective:
Evaluate the safety and efficacy of E-TRANS fentanyl, 25 mcg, for the management of post-operative pain following short-stay surgical procedures, during both the time after surgery during which the patient remains in the hospital and for an additional 26-hour period after discharge into a medically-supervised setting

Population:
Up to 375 adult patients admitted to the post-anesthesia care unit after a short-stay hospital procedure

Key inclusion criteria:
- Patients aged ≥18 years of either gender
- Patients admitted to the post-anesthesia care unit after undergoing a short-stay surgical procedure, an orthopedic procedure, a hernia repair or a proctological procedure, who are expected to be discharged from the hospital within 24 hours and for whom oral opioids would normally be prescribed for pain management in the hospital and/or at discharge from the hospital
- Patients awake and breathing spontaneously with oxygen saturation of 90% or greater and the ability to answer questions and follow commands
- Patients who have been titrated to comfort or who have remained comfortable for at least 30 minutes following their surgery

Key exclusion criteria:
- Expectation of postoperative analgesia supplied by a continuous regional technique
- Expectation of need for intensive care
- Requirement for another surgical procedure within 36 hours of the first procedure
- Use of intra-operative and/or post-operative administration of opioids other than morphine, fentanyl, sufentanil or alfentanil
- Known or suspected opioid tolerance

- History of opioid dependence

Study design:
A multi-center, open-label single-treatment trial

Study duration:
Up to 50 hours of E-TRANS use

Study conduct:
After recovery from intraoperative analgesia, patients were titrated to comfort using intravenous morphine, fentanyl, sufentanil, remifentanil or alfentanil. Patients who were eligible for study entry were then given an E-TRANS system and instructions for use. The protocol specified that at least one on-demand E-TRANS dose must be administered prior to discharge from the hospital into the medically supervised setting.

Patients were discharged from the hospital to a medically supervised setting consisting of rooms in a hotel near the hospital. A ACLS certified nurse with experience in opioid administration was stationed in an adjoining room. The nurse was to accompany the patient if the patient left the room for any reason.

During the study period, patients were assessed for level of pain intensity, number of on-demand doses required, oxygen saturation and vital signs.

Outcome measures:
The planned safety outcome measures were adverse events, respiratory function, vital signs, oxygen saturation and assessment of site reactions.

Study results:
Description of patients:
Twenty-seven patients were enrolled before the study was discontinued due to E-TRANS system technical failures. ALZA reports that [redacted] led to premature system shutdown after an undetermined period of use.

The enrolled patients included sixteen female patients and eleven male patients, twenty four of the enrolled patients were White. The surgeries included orthopedic surgery (n=9), lower abdominal surgery (n=1) thoracic/chest (n=7) and others e.g. tonsillectomy, right ear reconstruction, breast augmentation (n=10).

Twenty-one patients used two E-TRANS systems. Six patients applied three E-TRANS systems. Nineteen patients completed the study, staying in the medically supervised setting for 24 hours.

Sponsor's summary of deaths/discontinuations
No deaths were reported. Two people (300129, 302268) withdrew due to post-operative pain unrelieved by the E-TRANS system.

Protocol violations:
No protocol violations were reported.

Pharmacokinetics
No pharmacokinetic results were obtained from this study.

Efficacy
The sponsor did not perform an efficacy analysis since the time of system breakdown was unknown for all patients.

Safety
Analysis of safety results may be found in Section VII of this review, Integrated Review of Safety.

C-96-056
Title:
An open evaluation of safety and efficacy of E-TRANS (fentanyl) for management of postoperative pain in elderly postoperative patients.

Objective:
Evaluate the safety and efficacy of E-TRANS fentanyl, 25 mcg, for the management of moderate to severe pain in elderly postoperative inpatients who were expected to require treatment for at least 24 hours with an opioid analgesic

Population:
Up to 95 inpatients, aged 65 years old or more, who had undergone surgery

Key inclusion criteria:
- Inpatients aged ≥65 years of either gender
- At the time of initiation of post-operative analgesic management, patient must be of a clinical condition that would normally be considered suitable for IV PCA therapy at a participating study center
- Admission to the post-anesthesia care unit after having had general or regional anesthesia, who are expected to remain hospitalized and to have moderate to severe pain requiring parenteral opioids for at least 24 hours after their surgery
- Patients awake and breathing spontaneously with oxygen saturation of 93% or greater and the ability to answer questions and follow commands
- Patients who have been titrated to comfort for at least 30 minutes

Key exclusion criteria:
- Expectation of postoperative analgesia supplied by a continuous regional technique
- Expectation of need for intensive care
- Requirement for another surgical procedure within 36 hours of the first procedure
- Use of intra-operative and/or post-operative administration of opioids other than morphine, fentanyl, sufentanil or alfentanil

- Known or suspected opioid tolerance
- History of opioid dependence

Study design:
A multi-center, open-label single-treatment trial for up to three consecutive days

Study duration:
Up to 72 hours of use (3 days)

Study conduct:
After recovery from intraoperative analgesia, patients were titrated to comfort using intravenous morphine, fentanyl, sufentanil or alfentanil. Patients who were eligible for study entry were then given an E-TRANS system and instructions for use. The protocol specified that rescue medication was available during the first three hours after patch placement as needed for re-titration to comfort.

During the study period of up to 72 hours (three E-TRANS system applications), patients were assessed for level of pain intensity, number of on-demand doses required, oxygen saturation and vital signs.

Outcome measures:
The planned outcome measures were adverse events, respiratory function, vital signs, oxygen saturation and assessment of site reactions.

Study results:
Description of patients:
Eight patients were enrolled before the study was discontinued due to E-TRANS system technical failures. ALZA reports that [redacted] led to premature system shutdown after an undetermined period of use.

The enrolled patients included seven female patient and one male patient. The surgeries included orthopedic surgery (n=3), lower abdominal surgery (n=4) and thoracic/chest (n=1).

Seven patients completed the study by either using the device for 72 hours (n=1)or weaning off opioid analgesia (n=6).

The mean duration of study participation was 40 hours with a range of 6.8 to 72 hours. Three patients received one E-TRANS system and three patients used two E-TRANS systems. Two patients had three E-TRANS systems but one of them received no doses from the unit. The mean number of doses administered decreased with the third application (6.5) from the high of 15 doses during the second application. A mean of 13.9 doses were administered during the first administration.

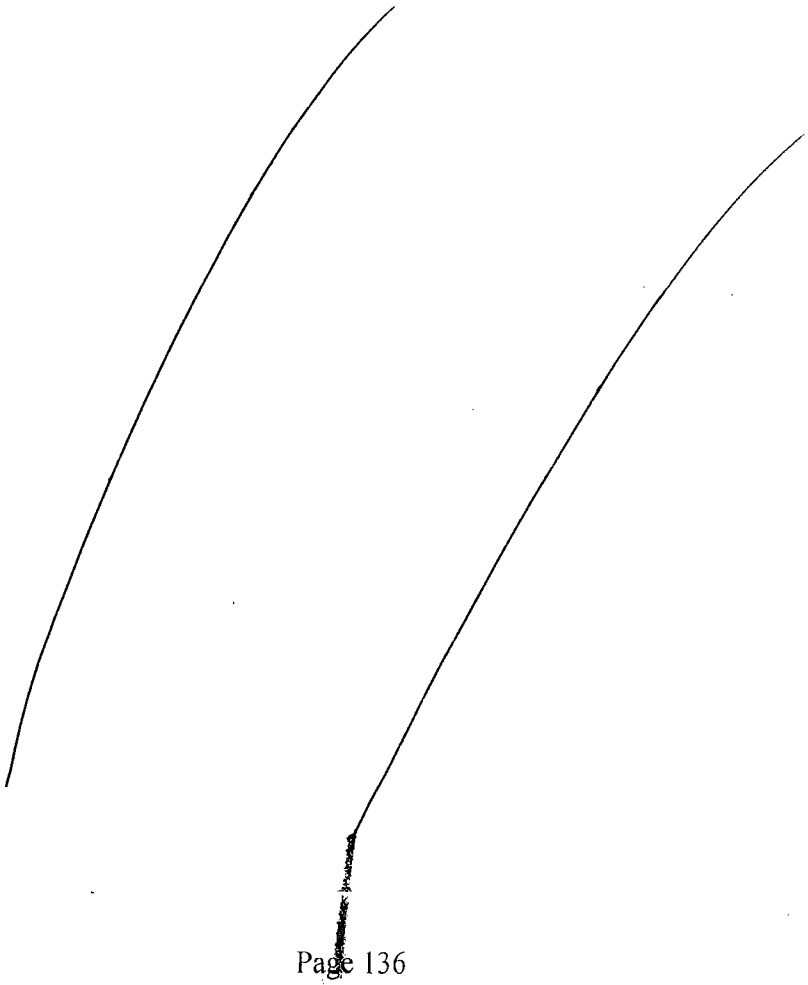
Sponsor's summary of deaths/discontinuations
No deaths were reported. One person (30040) withdrew due to severe post-operative pain unrelieved by the E-TRANS system.

Protocol violations:
No protocol violations were reported.

Pharmacokinetics
No pharmacokinetic results were obtained from this study.

Efficacy
The sponsor did not perform an efficacy analysis since the time of system breakdown was unknown for all patients.

Safety
Analysis of safety results may be found in Section VII of this review, Integrated Review of Safety.



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

_ § 552(b)(5) Deliberative Process

_ § 552(b)(4) Draft Labeling

C. Patients who discontinued for adverse events

Patient #	Age/sex	Adverse event (s)	Hrs on study
Study C-93-023			
Patient 207	71/M	Hypoxia, hypotension, stupor	14.5
Patient 231	45/F	Hypotension	7.5
Patient 257	38/F	Nausea	7.5
Study C-94-043			
Patient 1362	72/F	Pulmonary edema	24
Study C-94-057			
E-TRANS fentanyl			
Patient 30404	43/F	Nausea	3.2
Patient 30405	58/F	Rash	50
IV PCA morphine			
Patient 30039	30/F	Rash	50
Study C-94-058			
E-TRANS fentanyl			
Patient 30046	70/F	Nausea	32.8
Patient 30220	42/F	Ileus	45.4
Patient 30431	45/F	Postoperative bleeding	9.0
Patient 30598	66/M	Psychosis	39.1
IM morphine			
Patient 30050	57/M	Hypovolemia	39.5
Patient 30228	45/F	Postoperative bleeding	2.8
Patient 30320	69/F	Nausea,dizziness	16.9
Study C-94-059			
E-TRANS fentanyl			
Patient 30094	54/M	Pulmonary embolism	completed
E-TRANS placebo			
Patient 30136	54/F	Postoperative bleeding	18.0
Study C-95-016			
Patient 1081	53/F	Migraine, nausea	11.2
Patient 1101	38/F	Nausea, vomiting, headache	14.3
Study C-95-019			
Patient 127	30/F	Vomiting	19.8
Patient 166	19/F	Nausea, vomiting	19.6
Study C-2000-005*			
Patient 101	15/M	Nausea	24.3
Patient 103	14/F	Nausea	24.1
Patient 202	11/M	ASR-blistering at anode site	57.5
Patient 510	10/M	Nausea, vomiting	24.5
Patient 516	12/M	Nausea	19.0
Patient 602	12/F	ASR-pruritis, burning	53.4
Patient 603	7/M	Hallucinations	45.2

Patient #	Age/sex	Adverse event (s)	Hrs on study
Study C-2000-005*			
Patient 623	13/F	Hypoventilation	45.5
Patient 1001	14/F	Pruritis	48.0
Study C-2000-006			
Patient 206	66/F	Nausea/vomiting	46.3
Patient 604	77/M	Bladder spasms	3.1
Patient 605	68/M	Hypotension/shivering	2.8
Patient 610	76/F	Bladder spasms	4.8
Patient 819	78/F	Stupor	42.8
Study C-2000-007			
E-TRANS-fentanyl			
Patient 129	44/M	Pain at injection site	22.3
Patient 133	66/M	Confusion	9.0
Patient 206	56/F	Nausea and vomiting	26.3
Patient 315	46/M	Pruritis	3.8
Patient 318	58/F	Nausea/vomiting, Dyspnea, Tremors	6.5
Patient 351	79/M	Hypotension, chest pain, ventricular tachycardia	39.4
Patient 1101	42/F	Pain	3.1
Patient 1208	46/F	Pain	23.7
Patient 1917	41/F	ASR-pruritis	21.0
Patient 2217	43/M	Spasms of back muscles	21.0
Patient 2218	41/F	Restlessness	20.8
Patient 2220	35/F	Stoke, hemiparesis	15.3
Patient 2356	75/F	Headache	48.0
Patient 2367	41/F	Bleeding	20.8
Patient 2803	24/M	Pain	28.0
Patient 2901	36/F	Somnolence, nausea	18.1
Patient 3430	75/M	Confusion,tremor	19.8
Patient 3818	39/F	Nausea/vomiting	18.8
Patient 3901	32/F	Pruritis-chest/face	40.7
IV morphine			
Patient 122	74/F	Somnolence	1.5
Patient 136	83/F	Somnolence, hyoxia	25.3
Patient 146	53/F	Abdominal distention	69.6
Patient 205	41/M	Nausea	23.4
Patient 303	33/F	Chest numbness	16.1
Patient 1103	42/F	Pruritis, orbital edema, scleral reddening	19.8
Patient 1411	59/F	Ileus	42.3
Patient 1903	42/F	Migraine	20.7

Patient #	Age/sex	Adverse event (s)	Hrs on study
Study C-2000-007			
IV morphine			
Patient 2002	82/F	Confusion, agitation	25.0
Patient 2108	61/M	Nausea	24
Patient 2110	60/M	Fever	69.3
Patient 2319	39/F	Pruritis	13.3
Patient 2378	31/F	Bleeding, hypotension, tachycardia	9.4
Patient 2387	33/F	Hypoxia	65.5
Patient 2903	77/F	Hypoventilation, somnolence	4.9
Patient 3416	68/F	Distended abdomen	16.9
Patient 3814	72/F	Nausea	29.5
Patient 3827	30/F	Injection site discomfort	24.1
Patient 3904	32/F	Pruritis	21.4
Study C-2000-008			
E-TRANS-fentanyl			
Patient 411	42/F	Nausea	11.9
Patient 604	54/M	Back pain, hypertonia	4.8
Patient 614	63/F	Nausea	21.9
Patient 1212	42/F	Nausea	4.2
Patient 1302	20/M	Pruritis, nausea, vomiting, pain	20.7
Patient 1320	72/F	Somnolence, tremors	22
Patient 1402	50/F	Headache	19.5
Patient 1424	57/F	Dyspnea (subjective)	6.4
E-TRANS placebo			
Patient 602	71/M	Dizziness	15.2
Patient 1115	48/F	Pain	23.7
Patient 1208	61/F	Bladder spasms	4.4
Patient 1311	61/M	Sciatica	4.2
Patient 1324	72/M	Hypertonia	6.1
Study C-2000-009			
Patient 430	23/F	Urinary retention	11.5
Patient 517	45/M	Hypertension	5.7
Patient 532	61/F	Nausea/vomiting	20.3
Patient 1015	35/F	Nausea/vomiting	21.0
Patient 1314	20/F	ASR-burning	24.6
Patient 1333	64/M	Pain	23.4
Study C-2001-011			
E-TRANS-fentanyl			
Patient 901	76/M	Confusion	2.8
Patient 1452	26/F	Nausea	24
Patient 1760	66/M	Pruritis	21.7

Patient #	Age/sex	Adverse event (s)	Hrs on study
Study C-2001-011			
E-TRANS-fentanyl			
Patient 1819	68/M	Quadriplegia	4.5
Patient 1836	34/F	Insomnia	16
Patient 2002	58/F	Nausea	22.1
E-TRANS placebo			
Patient 207	30/F	Dyspnea	3.6
Patient 405	67/M	Pain	17.8
Patient 1722	45/F	Migraine, nausea	16.1

*All patients except 602, 623 and 1001 received 25 mcg of fentanyl. Patients 602, 623 and 1001 were increased to 40 mcg of fentanyl before being discontinued.

D. Patients who discontinued due to adverse events in studies of 48 or 72 hour duration

Studies of up to 48 hours			
Study	Age/sex	Reason	Hrs on study
Study 96-055	None		
Study 96-020	None		
Study C-95-019			
Patient 127	30/F	Vomiting	19.8
Patient 166	19/F	Nausea, vomiting	19.6
Study C-2000-009			
Patient 430	23/F	Urinary retention	11.5
Patient 517	45/M	Hypertension	5.7
Patient 532	61/F	Nausea/vomiting	20.3
Patient 1015	35/F	Nausea/vomiting	21.0
Patient 1314	20/F	ASR-burning	24.6
Patient 1333	64/M	Pain	23.4
Studies of up to 72 hours			
Study C-96-056	None		
Study C-94-043			
Patient 1362	72/F	Pulmonary edema	24
Study C-94-057			
E-TRANS fentanyl			
Patient 30404	43/F	Nausea	3.2
Patient 30405	58/F	Rash	50
IV PCA morphine			
Patient 30039	30/F	Rash	50
Study C-94-058			
E-TRANS fentanyl			
Patient 30046	70/F	Nausea	32.8
Patient 30220	42/F	Ileus	45.4
Patient 30431	45/F	Postoperative bleeding	9.0
Patient 30598	66/M	Psychosis	39.1
IM morphine			
Patient 30050	57/M	Hypovolemia	39.5
Patient 30228	45/F	Postoperative bleeding	2.8
Patient 30320	69/F	Nausea,dizziness	16.9
Study —	(Pediatric study)		
Patient 101	15/M	Nausea	24.3
Patient 103	14/F	Nausea	24.1
Patient 202	11/M	ASR-blistering at anode site	57.5
Patient 510	10/M	Nausea, vomiting	24.5
Patient 516	12/M	Nausea	19.0

Studies of up to 72 hours			
Study	Age/sex	Reason	Hrs on study
Study	(Pediatric study)		
Patient 602	12/F	ASR-pruritis, burning	53.4
Patient 603	7/M	Hallucinations	45.2
Patient 623	13/F	Hypoventilation	45.5
Patient 1001	14/F	Pruritis	48.0
Study C-2000-006			
Patient 206	66/F	Nausea/vomiting	46.3
Patient 604	77/M	Bladder spasms	3.1
Patient 605	68/M	Hypotension/shivering	2.8
Patient 610	76/F	Bladder spasms	4.8
Patient 819	78/F	Stupor	42.8

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/s/

Dawn McNeil
7/16/04 04:44:26 PM
MEDICAL OFFICER

Celia Winchell
7/16/04 04:52:55 PM
MEDICAL OFFICER
I concur with Dr. McNeil's recommendations. See my memo for further discussion of this application.

Bob Rappaport
7/23/04 07:01:57 PM
MEDICAL OFFICER
I agree in general with Dr. McNeil's conclusions. See my approvable memo dated July 23, 2004.