FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857 Tel:(301)827-7410

DIVISION DIRECTOR REVIEW AND BASIS FOR APPROVABLE ACTION

DATE: July 23, 2004

DRUG: E-TRANS (fentanyl HCl patient-controlled transdermal system)

NDA: 21-338

NDA Code: Type 3S NDA

SPONSOR: ALZA, Corp.

INDICATION:

ALZA, Corp. has submitted NDA 21-338 in support of marketing approval for their patient-controlled, transdermal, iontophoretic delivery system for fentanyl HCl. This drug-device combination product delivers 40 mcg of fentanyl HCl iontophetically over 10 minutes when activated, and incorporates a 10-minute lockout period between allowed activations. After a maximum of 80 doses, or after 24 hours, the device can no longer be activated. The device is composed of two layers. The top layer contains a 3-volt lithium battery and other electronic components. The bottom layer contains the skin adhesive and two hydrogel reservoirs, an anode containing fentanyl HCl and a cathode containing pharmacologically inactive materials. The E-TRANS system has been developed for institutional use only.

Review of the CMC portion of this application was completed by Rajiv Agarwal, Ph.D. Review of the pharmacology and toxicology data presented in this application was completed by Mamata De, Ph.D. Review of the clinical pharmacology and biopharmaceutics data in the application was completed by Srikanth Nallani, Ph.D. A statistical review and evaluation was completed by Milton Fan, Ph.D. Consultation on this application was obtained from the Center for Devices and Radiological Health, the

Controlled Substances Staff, the Division of Drug Marketing, Advertisement and Communications, and the Office of Drug Safety.

The sponsor has submitted four studies (C-95-016, C-2000-008, C-2001-011 and C-2000-007) in support of efficacy. A detailed review of these studies and of the clinical safety data was performed by D. Elizabeth McNeil, M.D. Celia Winchell, M.D. provided a secondary clinical review.

Efficacy:

Studies C-95-016 (016), C-2000-008 (008) and C-2001-011 (011): These three studies were single-application, randomized, placebo-controlled, double-blind, parallel-group trials comparing E-TRANS to placebo, performed in patients with post-operative pain. Subjects were adults requiring at least 24 hours of opioid treatment post-operatively, who were to have been titrated to a comfortable level of pain control with IV opioids in the PACU. Subjects were then randomized to receive a single application of E-TRANS or matching placebo for use during the first 24 hours post-operatively. IV fentanyl administration was permitted during the first three hours after study drug application. Subjects were considered to have completed the study after 24 hours from study drug application or after 80 doses had been delivered, whichever came first.

The primary efficacy outcome was defined as the 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 secondary outcome measures included: pain intensity, patient global assessment, investigator global assessment, number of on-demand doses delivered, number of patients requiring re-titration to comfort, and assessment of the adherence of the E-TRANS system.

The clinical reviews include thorough presentation and discussion of subject disposition. No significant concerns were identified. However, the protocol-defined analyses called for using an Evaluable population of subjects who discontinued only for lack of efficacy. Drs. McNeil and Winchell have also considered an ITT population in their analyses. This population consists of subjects who dropped out for any cause. I concur that this type of analysis is essential, as subjects who dropped out due to drug-related adverse events in particular should be considered treatment failures for a drug designed to treat a subjective symptom such as pain.

The table below, copied from page 7 of Dr. Winchell's review, summarizes the results of the primary efficacy analyses for the three trials.

Study #	Dropouts due to lack of efficacy			Dropouts for any reason		
	E-TRANS	Placebo	p-value	E-TRANS	placebo	p-value
C-95-016						
All-treated:	6/77 (8%)	9/25 (36%)	.0005	9/77 (12%)	12/25 (48%)	<.001
Evaluable:	6/77 (8%)	9/22 (41%)	.0001	9/77 (12%)	9/22 (41%)	.0017
C-2000-008						
All-treated:	48/154 (31%)	23/51 (45%)	.07	58/154 (38%)	29/51 (57%)	.0162
Evaluable	36/142 (25%)	19/47 (40%)	.0486	46/142 (32%)	25/47 (53%)	.0107
C-2001-011						
All-treated:	70/244 (29%)	144/240 (60%)	<.0001	90/244 (37%)	164/240 (68%)	<.0001
Evaluable:	64/235 (27%)	116/204 (57%)	<.0001	81/235 (35%)	128/204 (63%)	<.0001

These results demonstrate that E-TRANS provided a statistically significant greater treatment effect when compared to placebo in the analyses of both the Evaluable and ITT populations. The only exception occurred in Study 008, in the analysis of the ITT population. Dr. Winchell clearly explicates the only plausible cause for this finding in her review. A high drop-out rate during the first three hours of wear appeared to account for the failure of the study drug to separate from placebo. This finding seems to be at least partially explained by the inclusion of patients whose pain had not been adequately treated prior to system application. A post-hoc analysis performed by the review team that excludes these patients did find a statistically significant treatment effect for the study drug. On page 16 of her review, Dr. Winchell concludes that:

> ...the results of this study further highlight the need to emphasize that E-TRANS has been shown effective only in patients titrated to comfort prior to system application, and that a period of three hours of access to rescue medication is needed prior to reliance on the effectiveness of the transdermal system.

The secondary outcome measures were generally supportive of a finding of effective analgesia for E-TRANS.

Study C-2000-007 (007) was an open-label, active-control trial comparing E-TRANS to IV PCA morphine in the post-operative setting. E-TRANS did not show a statistically significant advantage over IV PCA morphine in the primary outcome measure, Patient Global Assessment at 24 hours. This open-label, active-control study did not provide adequate control for the introduction of bias. Nor did it provide assay sensitivity to allow for an adequate assessment of efficacy in the absence of a finding of superiority of the study drug. Therefore, it is, by design, inadequate to support a finding of efficacy.

Clinical Safety:

The overall safety database includes 1935 subjects exposed to E-TRANS. The following table, copied from page 21 of Dr. Winchell's review, summarizes the dose-by-duration data for subject exposure:

E-TRANS fentanyl exposure by time interval

Time Interval	Total	40 mcg	25 mcg
Number of subjects	1907	1142	765
<3 hours	36	28 (2.5%)	8 (1%)
≥3-24 hours	744	564 (49.4%)	180 (23.5%)
>24-≤48 hours	854	319 (27.9%)	535 (69.9%)
>48-<72 hours	243	206 (18%)	37 (4.8%)
>72 hours	30	25 (2.2%)	5 (0.6%)

The majority of the subjects who were treated with a 40-mcg system obtained 30 doses, with a range of 0 to 88 doses. Five hundred fifty subjects were administered two or more systems and obtained up to 225 doses.

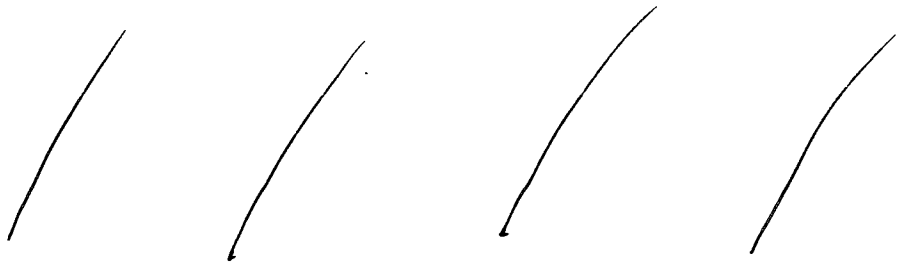
No subjects died during treatment with E-TRANS. Of the five subjects who died after completing or withdrawing from a study, two died of sepsis weeks after treatment. The other three subjects' deaths were attributed to pulmonary embolism and occurred between 2 and 7 days after treatment. E-TRANS does not appear to be a likely direct or indirect cause of these events.

The rates of discontinuation due to adverse events were similar in the E-TRANS and placebo groups, and higher in the morphine-treated groups. Serious adverse events and common adverse events were those that would be expected in post-surgical patients and/or patients treated with opiates. No unusual events or events occurring at a higher rate than would be expected in the post-surgical setting were found by the clinical review team, with the exception of application site reactions. These reactions were generally not severe and were reversible. However, the team correctly recommends that information regarding application site reactions should be provided to prescibers, especially in anticipation of the fact that patients may be treated consecutively with multiple systems, which could exacerbate these dermatologic effects.

Nonclinical Safety:

In her review, Dr. De notes that ALZA, Corp. has provided adequate data to support the nonclinical safety of their E-TRANS system. However, she has also recommended that the sponsor should reduce the specifications for the following impurities in the drug substance to NMT [redacted], or provide adequate qualification of their safety:

[redacted]



In addition, Dr. De has recommended that the sponsor should provide a limit of NMT [redacted] for [redacted] and [redacted] in the drug substance. This is due to the fact that these impurities are [redacted] and are structural alerts for mutagenicity. Alternatively, the sponsor may support the currently proposed levels for these impurities by demonstration that they are significant human metabolites, or by performing two in vitro genotoxicological studies that support adequate qualification of their safety.

Biopharmaceutics:

In his review, Dr. Nallani notes:

> Amount of fentanyl absorbed at treatment initiation is expected to be approximately 17 µg of the nominal dose of 40 µg. As the TRADENAME is repeatedly activated, the fentanyl dose absorbed approaches 40 µg. Two consecutive on-demand doses every hour produced 40 µg fentanyl dose absorption by the 12th hour or 25th dose. Upon repeated administration, steady state fentanyl levels were achieved at approximately 60 hours following two on-demand doses every 4 hours. These observations are consistent with accumulation of fentanyl.

ALZA, Corp. has developed an in vitro release method for determining the amount of fentanyl released upon E-TRANS system activation, using a new apparatus named [redacted]. Dr. Nallani has determined that the sponsor has adequately demonstrated in vitro in vivo correlation of the fentanyl dose delivered by the E-TRANS system for purposes of scale-up and post-approval changes to the drug product.

Chemistry, Manufacturing and Controls:

Dr. Agarwal describes the E-TRANS system operation on pages 9, 10 and 11 of his review. On page 10 of his review he provides the following discussion regarding product stability:

Originally the applicant proposed [redacted] of expiration date. The primary stability batches (registration lots) had a particularly high rate of out-of-box failures [redacted] which was also attributed to [redacted]. Therefore, corrective action lots (to-be-marketed batches) were manufactured [redacted] out [redacted] systems failed to deliver the required dose, or skipped doses. A total of [redacted] systems failed to pass electronic function test (Push button test). Stability data up to [redacted] is provided on corrective action lots, and the applicant requests a [redacted] of expiry from the date of manufacture. Analysis of the provided data only justify a [redacted] expiration date from the date of manufacture.

Numerous deficiencies in the comparability protocols for potential post-approval changes are outlined in a summary memo to the NDA file by Ravi Harapanhalli, Ph.D., Team Leader for the CMC review group.

Product Quality:

Adherence of the E-TRANS system was assessed as a secondary outcome in the pivotal efficacy studies. In Study 016, at the end of the 24-hour treatment period, fewer than 80% of the systems (total active and placebo units) were fully adherent. Five percent of the active systems had less than half of the unit adherent to the skin or required taping. Fourteen percent of the placebo systems required taping. In Studies 008 and 011, more than 90% of the systems were at least 90% adherent throughout the study. However, three of the active systems fell off during Study 008.

Other product quality issues have been extensive in the development program for E-TRANS. Technical failures caused some studies to be prematurely terminated and numerous premature subject discontinuations occurred in the pivotal efficacy studies. Technical failures included:

While the sponsor reports that some design features have been modified (and Agency review has confirmed this contention), others such as [redacted] continue to be the primary cause of product performance failure on stability testing. No data to support resolution of these problems have been submitted to date. In addition, as Dr. Winchell notes in her review, the design of the product continues to

—, leading to product failure. The sponsor states that a maximum of —of the systems will be non-functional by the end of the expiry period.

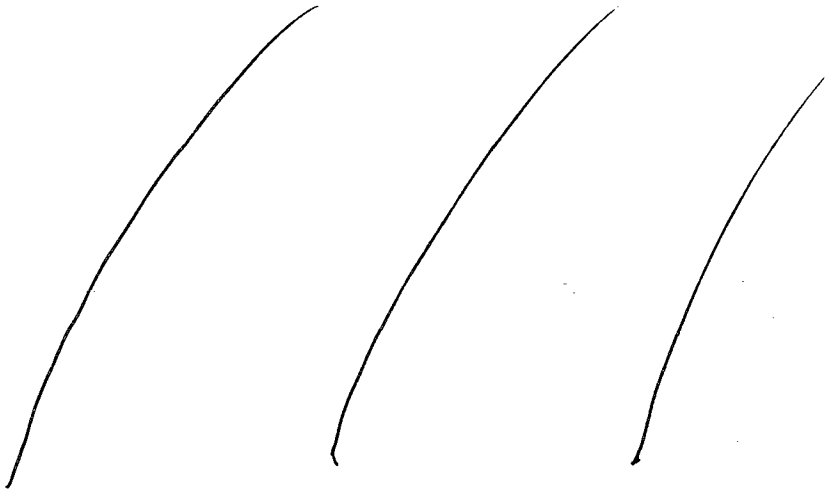
The sponsor has proposed a solution that includes labeling the product to require functionality testing by the pharmacist and/or health care provider prior to removing the product from the packaging. This testing process has not been adequately tested in the clinical setting. The sponsor has not fully delineated a plan that will allow non-functional systems to be secured and safely disposed of.

Issues Specific to CDRH:

The CDRH Compliance review staff found numerous deficiencies in the manufacturing of the E-TRANS system related to design controls, purchasing controls, and corrective and preventive action (CAPA). While inspection found that some of these concerns had been addressed, there appear to be numerous outstanding issues that raise significant safety concerns. These quality control concerns are exacerbated by the problems in product quality documented in the clinical trials.

Abuse Liability and Risk Management:

The three Divisions of the Office of Drug Safety have assessed the adequacy of the sponsor's proposed Risk Management Plan (RMP). Their concerns are delineated as follows:



1 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

Discussion

The sponsor has submitted data that appears to be adequate to support the efficacy of the E-TRANS system for the treatment of pain in post-operative patients from three to twenty-four hours after application of the product. However, the data only support efficacy when patients have had their pain adequately controlled during the first three hours after surgery, and when they have been provided with adequate pain control via other analgesic drug products during the first three hours after E-TRANS application. In addition, there are numerous product quality, patient and health-care provider use issues, and abuse liability concerns that have not been adequately addressed in this application.

The CMC and CDRH review teams have delineated substantial product quality concerns in their reviews. While the sponsor has proposed plans to address these deficiencies, some of those plans have yet to be implemented, and limited data has been submitted for Agency review. The sponsor notes that none of the apparent product quality concerns are likely to result in patients being exposed to excessive blood levels of fentanyl. However, reduced efficacy is, in and of itself, a safety concern for a narrow index, highly potent opioid such as fentanyl. If a patient experiences inadequate pain control in the post-operative setting due to product performance deficiencies, it is likely that that patient will request and be treated with additional, other opioid analgesics. In the event that the E-TRANS product continues to deliver fentanyl, albeit in lower than expected doses or with a delay in dosing, the patient could receive a toxic level of opioid medication, with the possibility of serious morbidity or death due to respiratory suppression. Additionally, inadequate analgesia in the post-operative patient is unacceptable, not only from an ethical standpoint, but due to the fact that it could result in patient agitation, with the potential for wound dehiscence or other post-surgical complications. Outside the clinical trial setting, access to "rescue" is not routinely provided because lack of efficacy is not anticipated. Also, the sponsor has not provided a clear paradigm for the disposal or return of failed units that will contain high doses of fentanyl. Nor have they adequately addressed patient and/or health care provider reimbursement for failed units. It should be noted that the data appear to support 100% product quality at approximately — stability testing, according to the CMC team's review of that data. However the failure rate is expected to rise rapidly after that to — of units at — and — at — months.

The use instructions for the E-TRANS system are complex. The purportedly simple technique of "depressing the button firmly twice within three seconds" may not be simple for a post-surgical patient suffering from severe pain and possible cognitive compromise due to the multiple medications used in the surgical and post-surgical setting, not to mention those patients with cognitive or physical limitations not related to the surgical setting. The use instructions for testing of the product prior to application are even more complicated. No data has been submitted with this application to support either patient ability to comply with the user instructions or health-care provider ability to comply with the product quality testing procedure in a busy post-surgical support setting. Definition

for appropriate patient selection has not been included in the product labeling. Use in blind or deaf patients has not been addressed, in spite of the requirement for patients to be aware of the beeping sound and the flashing lights. Although no patient/user problems were specifically identified in the clinical studies, those studies were not designed to address this concern, and the studies included a carefully selected patient population not likely to be comparable to the population that will be treated in the post-marketing setting.

The findings that efficacy appears to be limited to patients that have had their pain adequately controlled by IV PCA analgesia prior to E-TRANS application, and that additional analgesic administration appears to be necessary during the first three hours after product application, have been inadequately assessed in the clinical trials. This complex regimen appears to be necessary in order to provide even minimally acceptable and stable post-operative analgesia when using the E-TRANS system. Paradigms for conversion from IV PCA-, IV bolus-, IV infusion- or IM-analgesic dosing, to dosing with the E-TRANS system have not been explored. It is likely that some patients will require more than 24 hours of post-operative parenteral analgesic administration after surgery. The administration of more than a single E-TRANS unit post-operatively has not been adequately evaluated for durability of efficacy.

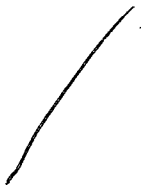
The clinical, CSS and ODS review teams have raised significant concerns regarding the abuse liability of the E-TRANS system and the adequacy of the sponsor's proposed Risk Management Plan (RMP). Fentanyl is a highly desirable drug of abuse, sought by substance abusers in and out of the health-care system. This product contains a total of 6.8 mg of fentanyl even after complete delivery of all allowable doses. The gel containing the fentanyl is easily removed from the device, and the fentanyl can then be easily extracted from the gel. The sponsor's proposed RMP does not provide for an adequate paradigm to assure that the residual fentanyl from these units will not find its way into the abuse community. This is complicated by the significant risk of product failure. No clear methodology that will ensure destruction of the residual fentanyl in failed units has been defined.

Serious adverse events occurring when family members activated the E-TRANS unit were reported in the clinical studies. The possibility of non-patient activation of the system raises additional safety concerns that must be considered in the overall risk to benefit analysis of the product. The product itself is small and unobtrusive, allowing for relatively easy diversion, or accidental failure to remove the unit prior to patient discharge.

Each of these points represents a significant concern by itself. Together they represent an extremely high level of abuse liability. The current RMP fails to fully address many of the concerns, and has not been adequately designed to reduce the risk of abuse liability to an acceptable level. While I do not think that it is plausible [redacted] as has been suggested by the ODS review team, the

RMP should include plans to address limiting promotion and distribution based on the proposed indication and use defined in the product labeling.

I do not agree with the CSS review team's recommendation that [redacted]



[redacted]. As a product administered under medical supervision and monitoring, the RMP (once complete) will address risk prevention when the product is used improperly or illegally.

Finally, there are numerous impurities in the drug substance that have not been adequately qualified. Two of these impurities are structural alerts for mutagenicity.

The safe use of this product cannot be assured due to an array of different problems associated with product development, manufacturing and use. These problems include:

- inadequate quality control
- complex patient and health care provider use instructions that have not been sufficiently assessed in clinical studies
- inadequate assessment of appropriate paradigms for conversion to other opiate analgesics and the use of adjunctive analgesic therapy during the apparent ineffective period after initial product application
- an extremely high abuse liability that has not been fully addressed with an appropriate plan for risk management; and
- potentially toxic impurities

APPEARS THIS WAY
ON ORIGINAL

Action recommended by the Division: Approvable

Bob A. Rappaport, M.D.
Director
Division of Anesthetic, Critical Care and Addiction Drug Products
Office of Drug Evaluation II, CDER, FDA

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Bob Rappaport
7/23/04 07:45:25 PM
MEDICAL OFFICER

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS

MEMORANDUM

DATE: July 15, 2004

TO: File, NDA 21-338

FROM: Celia Jaffe Winchell, M.D.
Medical Team Leader

RE: Supervisory Review of NDA 21-338, fentanyl HCl patient-controlled transdermal system ("E-TRANS")

1 BACKGROUND 3

2 EFFECTIVENESS 5

2.1 OVERVIEW 5
2.2 POPULATION 8
2.3 DESIGN AND ENDPOINTS 8
2.4 OUTCOME MEASURES AND ANALYTIC APPROACHES 8
2.5 RESULTS 9
2.5.1 Protocol C-95-016: The safety and efficacy of E-TRANS fentanyl (40 mcg on-demand) for the management of postoperative pain: A double-blind, single-center, placebo-controlled trial. 9
2.5.2 Protocol C-2000-008: The safety and efficacy of electrotransport (E-TRANS) fentanyl for the management of postoperative pain: A double-blind, multi-center, placebo-controlled trial. 13
2.5.3 Protocol C-2001-011: The safety and efficacy of electrotransport (E-TRANS) fentanyl 40 mcg for the treatment of postoperative pain: A double-blind, multi-center, placebo-controlled trial incorporating JCAHO pain management standards. 17
2.5.4 Efficacy Results 18

3 SAFETY 21

3.1 EXPOSURE 21
3.2 DEATHS 22
3.3 DISCONTINUATIONS 22
Overall, 66 of 1958 patients treated with E-TRANS fentanyl discontinued due to adverse events (3%). This is similar to the discontinuation rate due to adverse events in the placebo population, and slightly lower than the rate (5%) in the population treated with i.v. morphine. 23
3.4 SERIOUS ADVERSE EVENTS 23
3.4.1 Thromboembolic Events 24

3.5 COMMON ADVERSE EVENTS 24
3.6 ADVERSE EVENTS OF NOTE 27
3.6.1 Application Site Reactions *27*
3.6.2 Effects on Respiration and Oxygenation *28*
3.7 CLINICAL LABORATORY STUDIES, ECGS 28
3.8 SAFETY CONCLUSIONS 28

4 RISK MANAGEMENT CONCERNS 29

5 PRODUCT QUALITY ISSUES 29

6 CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS ISSUES 29

7 CONCLUSION AND RECOMMENDATIONS 30

1 BACKGROUND

NDA 21-338 for the fentanyl HCl patient-controlled transdermal system known during development as "E-TRANS" was submitted by Alza on 9/23/2003. The E-TRANS (fentanyl HCL) patient-controlled transdermal system is an iontophoretic device which uses low-level electricity to send the potent opioid, fentanyl, transdermally into the systemic circulation. The device is comprised of two layers. The top contains the 3 volt lithium battery and other electronic components. The bottom contains the skin adhesive and two hydrogel reservoirs: an anode containing fentanyl hydrochloride; a cathode containing pharmacologically inactive materials. E-TRANS permits patient controlled transdermal administration of a 40 mcg dose of fentanyl over 10 minutes, with a dosing interval of 10 minutes and a maximum of 80 delivered doses per device. By design, the device is to cease functioning 24 hours after the first dose, or after 80 doses have been delivered, whichever comes first.

Fentanyl is a potent opioid marketed as an analgesic and as an adjunct to anesthesia in parenteral, transmucosal, and transdermal forms. The common side effects of fentanyl include nausea, vomiting, constipation, somnolence, and diaphoresis. The most serious risk is respiratory depression. Currently marketed transdermal formulations provide analgesic doses over a period of several days at a constant rate. These products (Duragesic™ and generics) are used in outpatients and are generally deemed unsuitable for post-operative use due to the imprecision of titration of such delivery systems, and observed cases of overdose in post-operative patients. Although E-TRANS employs a transdermal route of administration, the patient-control feature is envisioned to allow more careful titration, and positions E-TRANS as an alternative to intravenous patient-controlled analgesia (PCA). Conversely, the large dose of fentanyl included in each system and the potential for overdose led the Division to deem the product suitable only for use in monitored settings.

Therefore, this application concerns the 40 mcg dose only.

The application is based on 28 studies, 4 of which were completed, controlled safety and efficacy studies. Six studies were terminated early due to technical difficulties. Overall, 2660 patients participated in these studies, 1142 of whom received the E-TRANS 40 mcg system. The remainder received the 25 mcg E-TRANS system, a placebo or an active control. Other studies not included in the safety database include pharmacology studies in healthy volunteers using developmental formulations, a study of IV PCA fentanyl, and "wearing" studies involving a placebo system.

The clinical studies of the effectiveness and safety of this product have been reviewed by D. Elizabeth McNeil, M.D. The application has also been reviewed by Milton Fan, Ph.D. (biostatistics), Srikanth Nallani, Ph.D. (clinical pharmacology and biopharmaceutics), Rajiv Agarwal, Ph.D., (chemistry), Mamata De, Ph.D. (pharmacology/toxicology), and a review team from the Center for Devices and Radiological Health. In this memo, I will briefly review the effectiveness and safety data summarized in the primary clinical

review, as well as any relevant information found in the primary reviews from the other disciplines, and make appropriate recommendations for action on the NDA.

APPEARS THIS WAY
ON ORIGINAL

2 EFFECTIVENESS

2.1 Overview

Evidence of efficacy has been submitted in the clinical studies C-95-016; C-2000-008; and C-2001-011. An active-control, open-label comparison to IV PCA morphine (C-2001-007) was also identified as pivotal by the sponsor, but due to design issues was not deemed suitable for providing evidence of efficacy. Although it is discussed at some length in the primary clinical and statistical reviews, I have not included it in this memo.

The table below briefly summarizes the features of the studies reviewed for efficacy in this memorandum.

Protocol # and Title	Design
C-95-016 "The safety and efficacy of E-TRANS fentanyl (40 mcg on-demand) for the management of postoperative pain: A double-blind, single-center, placebo-controlled trial."	Single center (New Zealand), randomized, double-blind, placebo-controlled, parallel groups **N** = 102 (77 active/25 placebo) **Dose**: E-TRANS 40 mcg vs. placebo **Duration**: 24 hours (single application of E-TRANS system) **Result: Evidence of efficacy for E-TRANS based on rate of dropout due to lack of efficacy, supported by analysis of all-cause dropout rate.**
C-2000-008 "The safety and efficacy of electrotransport (E-TRANS) fentanyl for the management of postoperative pain: A double-blind, multi-center, placebo-controlled trial."	10 US centers, randomized, double-blind, placebo-controlled, parallel groups N = 205 (154 active/51 placebo) **Dose:** E-TRANS 40 mcg vs. placebo **Duration:** 24 hours (single application of E-TRANS system) **Result: Evidence of efficacy for E-TRANS based on rate of dropout due to lack of efficacy; supported by analysis of all-cause dropout rate. Marginal significance of primary analyisis strengthened by post-hoc subset analysis excluding patients inadequately titrated to comfort prior to randomization.**
C-2001-011 "The safety and efficacy of electrotransport (E-TRANS) fentanyl 40 mcg for the treatment of postoperative pain: A double-blind, multi-center, placebo-controlled trial incorporating JCAHO pain management standards."	20 centers, randomized, double-blind, placebo-controlled, parallel groups N = 488 (244 active/240 placebo) **Dose:** E-TRANS 40 mcg vs. placebo **Duration:** 24 hours (single application of E-TRANS system) **Result: Evidence of efficacy for E-TRANS based on rate of dropout due to lack of efficacy. Supported by analysis of all-cause dropout rate.**

Blank
Page

The table below summarizes the results of the three studies demonstrative of efficacy, showing the rate of discontinuation for lack of efficacy and the all-cause dropout rate for each study. Although the discontinuation rate for lack of efficacy was the protocol-specified primary endpoint, from the standpoint of defining the risk/benefit ratio, it is also important to consider subjects who dropped out for other reasons (most importantly, drug-related adverse events) as treatment failures. Therefore, the all-cause dropout rate is relevant. The protocol-specified analysis used the "evaluable" subset, defined as patients remaining in the trial for at least three hours, to the end of the window during which p.r.n. rescue with i.v. fentanyl was permitted. For these analyses, both the evaluable population and the all-treated population are displayed.

	Dropouts due to lack of efficacy			Dropouts for any reason		
Study #	E-TRANS	Placebo	p-value	E-TRANS	placebo	p-value
C-95-016						
All-treated:	6/77 (8%)	9/25 (36%)	.0005	9/77 (12%)	12/25 (48%)	<.001
Evaluable:	6/77 (8%)	9/22 (41%)	.0001	9/77 (12%)	9/22 (41%)	.0017
C-2000-008						
All-treated:	48/154 (31%)	23/51 (45%)	.07	58/154 (38%)	29/51 (57%)	.0162
Evaluable	36/142 (25%)	19/47 (40%)	.0486	46/142 (32%)	25/47 (53%)	.0107
C-2001-011						
All-treated:	70/244 (29%)	144/240 (60%)	<.0001	90/244 (37%)	164/240 (68%)	<.0001
Evaluable:	64/235 (27%)	116/204 (57%)	<.0001	81/235 (35%)	128/204 (63%)	<.0001

Patients were excluded from the evaluable population for dropout during the first three hours (when i.v. fentanyl was available to both groups on demand).

As shown in the table above, whether considering all-treated or the evaluable subset, and whether considering dropouts for lack of efficacy or all-cause discontinuations, Studies C-95-016 and C-2001-011 demonstrate an effect of E-TRANS. For Study C-2000-008, the analysis of dropout due to lack of efficacy in the all-treated population did not show superiority of E-TRANS over placebo. However, examination of the data revealed that a substantial number of the patients were not adequately titrated to comfort during the 3 hour period of prn availability of i.v. fentanyl. Although pain scores were collected in the post-anesthesia care unit, the protocol did not stipulate a definition of titration to comfort based on PACU pain score. A post-hoc analysis including only those subjects who were successfully titrated to comfort yielded a statistically significant difference in the rate of discontinuation due to lack of efficacy between the E-TRANS and placebo-treated groups (25% vs 44%). The subsequent study (C-2001-11) included a protocol-specified maximum PACU pain score allowable for study entry.

Therefore, when this appropriate, albeit post-hoc, subset analysis is considered, all three studies demonstrate efficacy of E-TRANS for the first 24 hours post-op, in patients *who have been titrated to comfort prior to PACU discharge and patch application, who have been given access to i.v. fentanyl for three hours after patch application.*

2.2 *Population*

All studies had similar inclusion and exclusion criteria. Patients were awake, spontaneously-breathing, post-operative adults of ASA status I-III, with expectation of moderate to severe pain requiring at least 24 hours of opioid treatment post-operatively. To be eligible, patients had to be in the PACU at least 30 minutes and were to have been comfortable or titrated to comfort with i.v. opioids. Patients were ineligible if post-operative analgesia was to be supplied by a continuous regional technique, and in Studies 2000-008 and 2001-011, patients were ineligible if they had received intra-operative or post-operative administration of opioids other than morphine, fentanyl, sufentanil or alfentanil. Patients who were anticipated to require intensive care or additional surgery within 36 hours were also ineligible.

2.3 *Design and Endpoints*

Study designs were very similar. All studies involved a single application of E-TRANS or matching placebo for use during the first 24 hours post-operatively. Patients were to be randomized after receiving routine care in the PACU, and determined to be eligible. Study C-95-016 stipulated specifically that patients were to be titrated to comfort using i.v. morphine, fentanyl, sufentanil, or alfentanil. Study C-2000-008 stipulated that patients were to be "awake, alert, and comfortable." Study C-2001-011 required a PACU pain score of <5 for randomization, and also noted that patients requiring more than the equivalent of 40 mg morphine sulfate or 400 mcg fentanyl to achieve titration to comfort should be reassessed for appropriateness for post-op PCA. Pain intensity, vital signs and oxygen saturation were to be assessed just prior to application of the study system. 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 was allowed as rescue medication during the first three hours after study system application.* During the study period, assessments included pain intensity, number of on-demand doses, patient and investigator global assessments, vital signs, oxygen saturation, and E-TRANS system adherence.

Patients were considered to have completed the study after the E-TRANS system was worn for the study period of 24 hours or after 80 on-demand doses (the maximum number of doses/system) had been delivered, whichever came first. Patients were to be withdrawn from the study for inadequate pain control, technical failure of device, or adverse events. Study C-2001-011 also stipulated that patients would be terminated if they no longer required analgesia, or were discharged from the hospital.

2.4 *Outcome Measures and Analytic Approaches*

The protocol-specified primary analysis was the 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 included: pain intensity, patient global assessment, investigator global assessment, number of on-demand doses delivered, number of patients requiring re-titration to comfort, and assessment of the adherence of the E-TRANS system. I have focused primarily on the discontinuation rate

in the summaries below because I believe it captures aspects of pain and patient satisfaction. However, poor pain control or dissatisfaction may have occurred without dropout in some cases, so these measures provide some reassurance of efficacy. They are presented only briefly below but analyzed more completely in Dr. McNeal's and Dr. Fan's reviews.

Although the discontinuation rate for lack of efficacy (inadequate pain control) was the protocol-specified primary endpoint, from the standpoint of defining the risk/benefit ratio, it is also important to consider subjects who dropped out for other reasons (most importantly, drug-related adverse events) as treatment failures. Therefore, the all-cause dropout rate is relevant and I have presented it in the summaries below, using information from Dr. McNeal's and Dr. Fan's reviews. In addition, although the protocol-specified primary analysis called for an evaluable subset (defined as patients remaining in the trial for at least three hours, to the end of the window during which p.r.n. rescue with i.v. fentanyl was permitted), arguably an intent-to-treat analysis would be informative as well. Therefore, I have presented an all-treated analysis in the summaries below.

2.5 Results

The results of the three double-blind, placebo-controlled efficacy trials, as documented in Dr. McNeal's review, are briefly summarized below:

2.5.1 Protocol C-95-016: The safety and efficacy of E-TRANS fentanyl (40 mcg on-demand) for the management of postoperative pain: A double-blind, single-center, placebo-controlled trial.

2.5.1.1 Demographics and Patient Disposition

Over 80% of the patients were female, with a median age of 45. The treatment groups differed somewhat at baseline with respect to ASA status and surgical site. More ASA II and III patients were included in the E-TRANS group (~28% vs 18% in the placebo group). Approximately 79% of the E-TRANS group had undergone abdominal surgery and 21% had undergone orthopedic surgery, while the placebo group was comprised of 68% abdominal surgery and 32% orthopedic surgery patients. Mean pain intensity was slightly higher in the group randomized to placebo than in the group randomized to E-TRANS at both time 0 (baseline, E-TRANS mean VAS 31.6 ± 1.51 vs placebo 36.5 ± 2.85) and at the end of the three-hour window during which i.v. fentanyl was provided p.r.n. (E-TRANS mean VAS 31.8 ± 1.99 vs placebo 36.1 ± 4.28). This baseline imbalance in pain intensity might be expected to bias the study in favor of E-TRANS on the primary endpoint, dropout due to lack of efficacy. However, the imbalance in ASA status might tend to bias the study in favor of placebo on the all-cause dropout analysis, as this more fragile population might be prone to a wider range of reasons for discontinuation.

Patient disposition is illustrated in the table below, from Dr. McNeal's review:

Patient disposition for study C-95-016

Disposition	Total	E-TRANS fentanyl	Placebo
Patients screened	144		
Patients enrolled	102	77	25
Patients who discontinued	21	9 (11.7%)	12 (48%)
Inadequate pain control	15		
Discontinuation at ≤3 hours		0	0
Discontinuation at >3 hours		6 (7.8%)	9 (36%)
Adverse events	2	2 (2.6%)	0
Erroneous early system removal	1	1 (1.3%)	0
Suspected system failure	3	0	3 (12%)
Patients who completed the study	81	68 (88%)	13 (52%)

The only protocol violations deemed significant by the primary reviewer included a patient randomized to E-TRANS who had elastoplast allergy (an exclusion criterion), and a patient randomized to placebo who received off-protocol rescue during hour 5. This patient was ultimately withdrawn due to inadequate pain control and therefore the outcome of the study was unaffected.

2.5.1.2 Efficacy Results

2.5.1.3 Discontinuations due to inadequate pain control

The protocol-specified primary outcome measure was the rate of discontinuation due to inadequate pain control. The sponsor defined this measure as the number of patients in each treatment group who dropped out of the study more than three hours after application of study therapy due to inadequate pain control. The evaluable population was defined as patients remaining in the trial for at least three hours, to the end of the window during which p.r.n. rescue with i.v. fentanyl was permitted. The original protocol specified the use of the evaluable population for the primary efficacy analyses instead of an intent-to-treat population. The discontinuation rate due to inadequate pain control (at any time) in all-treated patients is also shown in the table below. In this study, discontinuations during the first three hours were limited to three patients in the placebo group, all of whom discontinued due to "suspected technical failure." Therefore, the number of discontinuations due to inadequate pain control is the same in the all-treated (ITT) and evaluable populations. The results for both analyses are shown in the table below.

Discontinuations due to Inadequate Pain Control, Study C-95-016

	E-TRANS	Placebo	p-value
Evaluable:	6/77 (8%)	9/22 (41%)	.001
All-treated:	6/77 (8%)	9/25 (36%)	.0005

2.5.1.4 Discontinuations for any reason

Because focus on discontinuations due to lack of efficacy implicitly assumes a favorable outcome to discontinuations for other reasons, it is possible that an effective but poorly tolerated product might appear superior to placebo if few subjects terminated for lack of efficacy, but many terminated due to adverse events. Similarly, ignoring discontinuations due to "technical failures" tends to overstate the product's efficacy, as subjects discontinuing for this reason cannot be considered treatment successes. Therefore, the all-cause discontinuation rate may be a better reflection of the overall effect of the product. As shown in the patient disposition table above, in this study, there were relatively few dropouts for adverse event (all in the E-TRANS group), and the "technical failures" occurred early and did not affect the analysis of the evaluable population. The rates of dropout for any reason are shown in the table below.

Discontinuations for Any Reason, Study C-95-016

	E-TRANS	placebo	p-value
Evaluable:	9/77 (12%)	9/22 (41%)	.0017
All-treated:	9/77 (12%)	12/25 (48%)	<.001

2.5.1.4.1 Secondary endpoints

Secondary endpoints analyzed included.

- Pain intensity
- Patient global assessment
- Investigator global assessment
- Number of on-demand doses delivered
- Number of patients requiring re-titration to comfort

As documented in Dr. McNeal's review, analyses of the secondary endpoints supported the conclusion of efficacy for E-TRANS.

The adherence of the E-TRANS system was also assessed. At the end of the 24 hour treatment period, fewer than 80% of the systems were fully adherent. Of the active systems, 5% had less than half the system adherent to the skin or had required taping. Of the placebo systems, 14% required taping.

Dr. McNeal also examined the use of i.v. fentanyl during the first three hours after the system was applied. Patients who experienced inadequate pain control during the first three hours after initiating use of the study system were allowed to receive intravenous rescue doses of fentanyl. The use of this rescue medication was similar in the active and placebo groups. In the active group, 33.8% (n=26) of the participants required rescue medication. The mean cumulative rescue fentanyl dose in this group was 78.5 mcg (range 20-220 mcg). In the placebo group, 36.4% (n=8) of the participants required rescue medication. The mean cumulative rescue fentanyl dose in this group was 76.3 mcg (range 20 to 180 mcg). As Dr. McNeal concludes, the E-TRANS group clearly had inadequate analgesia supplied by the system alone, because their use of rescue fentanyl was no less

than that in the placebo group. The efficacy analysis addresses only dropouts for lack of efficacy *after* the first three hours (i.e., after the period during which rescue was available). Therefore, conclusions about the efficacy of the E-TRANS system apply to its ability to control pain *only after a three-hour period during which i.v. rescue drug is available.*

2.5.1.5 Efficacy Conclusion, Study C-95-016

This study has demonstrated efficacy of the E-TRANS fentanyl system in comparison to placebo for a single 24-hour application period in patients who have been successfully titrated to comfort with parenteral opioids prior to system application, and have been provided with access to i.v. rescue medication for the first three hours of system use.

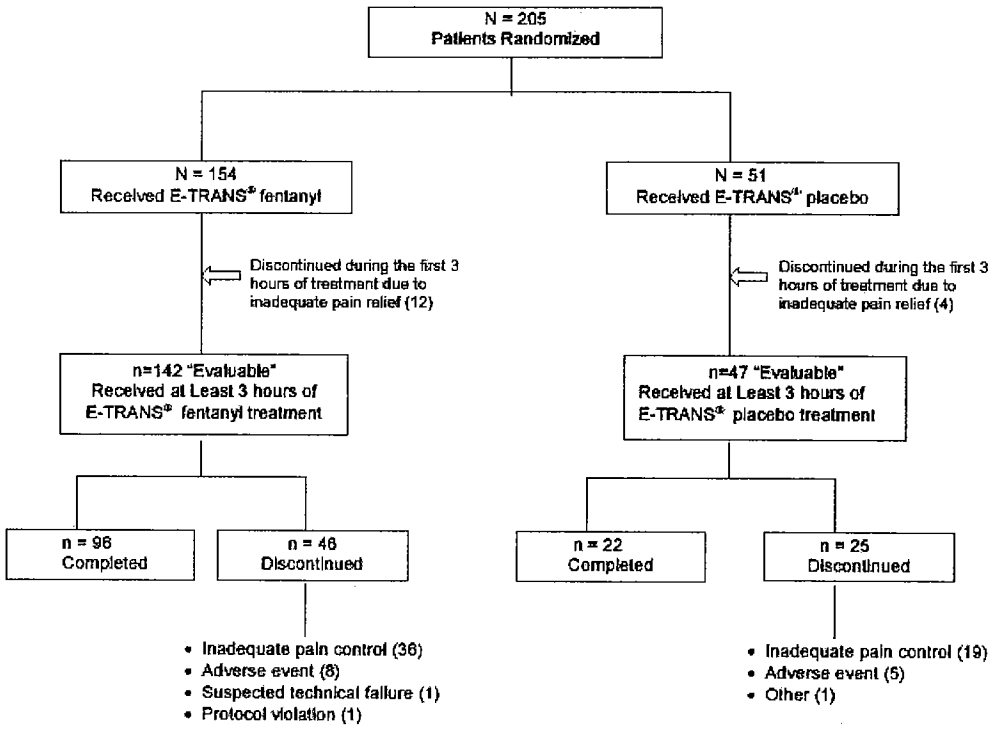
APPEARS THIS WAY
ON ORIGINAL

2.5.2 Protocol C-2000-008: The safety and efficacy of electrotransport (E-TRANS) fentanyl for the management of postoperative pain: A double-blind, multi-center, placebo-controlled trial.

2.5.2.1 Demographics and Patient Disposition

Of the 189 patients in the evaluable population, 69% were female and the median age was 49. The groups were generally similar at baseline, although the placebo group had a higher median age (57 vs. 49 in the E-TRANS group). No obvious differences in type of surgery or ASA status were noted. Pain scores were similar at baseline (mean VAS 45.9 ± 2.25 in the E-TRANS group vs. 46.0 ± 3.07 in the placebo group), but differed by the end of the three-hour period in which i.v. fentanyl rescue was available (mean VAS 33.3 ±2.27 in the E-TRANS group vs. 41.9 ±4.36 in the placebo group).

Patient disposition is illustrated in the diagram below, from Dr. McNeal's review:



Source: Tables 11.2.2-1 and 11.3.2-1.

Protocol violations deemed significant by the primary reviewer included 6 patients (4 on E-TRANS, 2 on placebo) who received prohibited analgesics while on study. Because of the unequal randomization, this represents even distribution of these protocol violators across treatment arms and is unlikely to affect study results.

2.5.2.2 Efficacy Results

2.5.2.3 Discontinuations due to inadequate pain control

The protocol-specified primary outcome measure was the number of patients in each treatment group who dropped out of the study more than three hours after application of study therapy due to inadequate pain control. The discontinuation rate due to inadequate pain control (at any time) in all-treated patients is also shown in the table below. In this study, 8% of each group discontinued during the first three hours due to inadequate analgesia. One discontinuation during the first three hours occurred in the placebo group for reasons other than inadequate analgesia.

Furthermore, although the primary endpoint was prespecified in the protocol as described above, the sponsor's examination of the data revealed that a substantial number (39/205, 19%) of the patients were not adequately titrated to comfort during the 3 hour period of p.r.n. availability of i.v. fentanyl. Although pain scores were collected in the post-anesthesia care unit, the protocol did not stipulate a definition of titration to comfort based on PACU pain score. A post-hoc analysis including only those subjects who were successfully titrated to comfort was undertaken, using the subset of patients who had a pain score of <75 on a 100-point scale prior to randomization.

The results for these analyses are shown in the table below.

Discontinuations due to Inadequate Pain Control, Study C-2000-008

	E-TRANS	Placebo	p-value
Evaluable:	36/142 (25%)	19/47 (40%)	.0486
All-treated:	48/154 (31%)	23/51 (45%)	.07
Patients with PACU pain score <75	30/121 (25%)	20/45 (44%)	.014

2.5.2.4 Discontinuations for any reason

As discussed above, the all-cause discontinuation rate may be a better reflection of the overall effect of the product. As shown in the patient disposition diagram above, in this study, 8/154 (5%) of the E-TRANS group and 5/51 (10%) of the placebo group discontinued prematurely due to adverse events. One "technical failure" was a reason for discontinuation in the E-TRANS group. The rates of dropout for any reason are shown in the table below.

Discontinuations for Any Reason, Study C-2000-008

	E-TRANS	placebo	p-value
Evaluable:	46/142 (32%)	25/47 (53%)	.0107
All-treated:	58/154 (38%)	29/51 (57%)	.0162

2.5.2.5 Secondary Endpoints

Other endpoints evaluated included pain intensity (0-100 VAS), and investigator and patient global assessments. The protocol specified analysis of mean pain intensity over the 24-hour treatment period, defined as the mean of the available VAS measurements after Hour 0 and during the 24 hour treatment period for a given patient. The VAS was considered missing when the patient was asleep. In the case of premature discontinuation, the mean pain intensity was to be computed only up to the time of removal. However, Alza noted upon analyzing the data that approximately 20% of the protocol-specified pain measurements were missing, and therefore performed an analysis comparing the last pain intensity score, rather than the mean pain score over the 24 hours. In this analysis, no statistically significant difference was seen between the treatment groups when the all-treated population was analyzed. The evaluable subset and the PACU score <75 subset, however, differed significantly on this measure. On the investigator global assessment, the proportion of patients rated successful was statistically significantly higher in the E-TRANS group than the placebo group in all analysis populations. However, on the patient global, only the PACU score <75 subset demonstrated superiority of E-TRANS over placebo.

The adherence of the E-TRANS system was also assessed. More than 90% of the systems were at least 90% adherent throughout the study. Three systems (active) fell off during the study.

2.5.2.6 Technical Failures

Although technical failure was cited as a reason for discontinuation by only one patient, technical failures were reported 6 of 154 (4%) active E-TRANS systems used in the study and 4 of 55 (7%) placebo systems.

2.5.2.7 Efficacy Conclusion, Study C-2000-019

On the primary endpoint, discontinuation due to lack of efficacy after three hours of wear, E-TRANS was superior to placebo, with 25% of subjects discontinuing due to inadequate analgesia, vs. 40% in the placebo group. Dr. McNeal examined the reasons for discontinuation across treatment arms, and noted that lack of efficacy accounted for 36/48 (78%) of the discontinuations in the E-TRANS group and 19/25 discontinuations (76%) in the placebo group. Because of this observation, she concludes that this trial has failed to demonstrate the efficacy of E-TRANS. I cannot agree with this interpretation of the data. The reasons for discontinuation are a problem of competing risks: if there are fewer discontinuations for technical failure, withdrawal of consent, adverse events, or any other reason, the proportion citing lack of efficacy as the reason for discontinuation becomes higher. Very few patients discontinued E-TRANS use for adverse events; indeed, more patients in the placebo group discontinued due to adverse events than in the E-TRANS group. Rather than arguing against the benefit of E-TRANS by citing the primacy of lack of efficacy as a reason for discontinuation, I note conversely that the product provided adequate analgesia for 75% of the patients, and that it presented few reasons to discontinue its use to any participants other than the 25% for whom it was ineffective. The high rate of discontinuation during the first three hours of wear

accounted for the failure of the drug to separate from placebo in the all-treated analysis of dropouts for inadequate analgesia. This appears to be at least partially explained by the erroneous inclusion of patients whose pain had not been adequately treated in the PACU prior to system application. The subset analysis excluding these patients, albeit post-hoc, is appropriate and supports the conclusion of efficacy of E-TRANS. However, the results of this study further highlight the need to emphasize that E-TRANS has been shown effective only in patients titrated to comfort prior to system application, and that a period of three hours of access to rescue medication is needed prior to reliance on the effectiveness of the transdermal system.

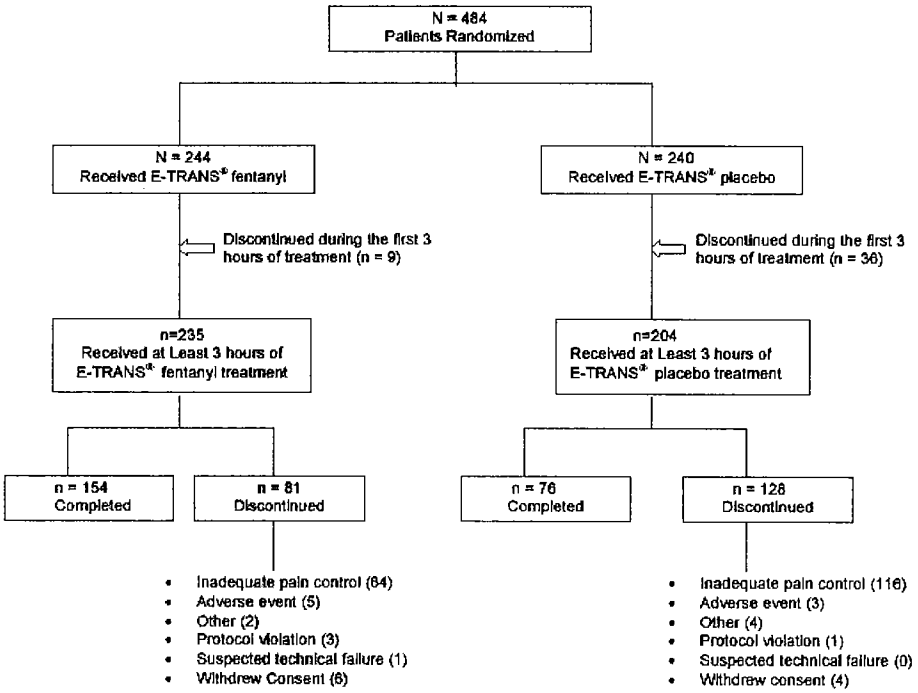
This study has demonstrated efficacy of the E-TRANS fentanyl system in comparison to placebo for a single 24-hour application period in patients who have been successfully titrated to comfort with parenteral opioids prior to system application, and have been provided with access to i.v. rescue medication for the first three hours post surgery.

2.5.3 Protocol C-2001-011: The safety and efficacy of electrotransport (E-TRANS) fentanyl 40 mcg for the treatment of postoperative pain: A double-blind, multi-center, placebo-controlled trial incorporating JCAHO pain management standards.

2.5.3.1 Demographics and Patient Disposition

The patients enrolled in this study were predominantly female (70% in each group), with a median age of 54 (each group). The treatment groups were very similar at baseline with the exception of a slight imbalance with respect to ASA status. More ASA III patients were included in the placebo group (28% vs 18% in the E-TRANS group), while more ASA II patients were included in the E-TRANS group (72% vs 59% in the placebo group). Baseline pain scores were similar at time 0 (VAS pain score, mean ±SEM of 3 ± .08 vs 3.1 ± .08), but slightly different at the end of the 3-hour window during which rescue was available (3.3 ± 0.13 vs 3.9 ± 0.18)

Patient disposition is illustrated in the diagram below, from Dr. McNeal's review:



Source: Tables 11.2.2-1 and 11.3.2-1.

A total of 131 protocol violations were recorded in the E-TRANS group and 116 in the placebo group. However, the substantial majority of these were characterized as "procedural," defined as assessments/evaluations done out of order, out of window, or not done. Protocol violations deemed significant by the primary reviewer included patients who received prohibited medications intraoperatively or post-operatively

(opioids other than fentanyl during the first 3 hours post-op, opioids given after the first 3 hours, non-opioid prohibited pain medication). Of the affected patients, however, most did not complete the three-hour post-op window and were therefore not included in the evaluable population. Ultimately, 13 E-TRANS and 9 placebo patients who received prohibited medications during the trial were included in the evaluable population. Analyses re-categorizing those patients as early discontinuations due to inadequate analgesia or excluding them from analysis altogether did not affect the results of the study.

2.5.4 Efficacy Results

2.5.4.1 Discontinuations due to inadequate pain control

The protocol-specified primary outcome measure was the 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 or placebo. The discontinuation rate due to inadequate pain control (at any time) in all-treated patients is also shown in the table below. In this study, discontinuations in the first three hours occurred more commonly in the placebo group than in the E-TRANS group (as shown in the diagram above). Of the 9 patients in the E-TRANS group who discontinued early, 6 of these cited inadequate analgesia. In the placebo group, 28 of the 36 discontinuations during the first three hours were due to inadequate analgesia. The results for both analyses are shown in the table below.

Discontinuations due to Inadequate Pain Control, Study C-2001-011

	E-TRANS	Placebo	p-value
Evaluable:	64/235 (27%)	116/204 (57%)	<.0001
All-treated:	70/244 (29%)	144/240 (60%)	<.0001

2.5.4.2 Discontinuations for any reason

As discussed above, the all-cause discontinuation rate may be a better reflection of the overall effect of the product. As shown in the patient disposition diagram above, in this study, there were relatively few dropouts for adverse event (5/244 (2%) in the E-TRANS group vs 3/240 (1%) in the placebo group. The rates of dropout for any reason are shown in the table below.

Discontinuations for Any Reason, Study C-95-016

	E-TRANS	placebo	p-value
Evaluable:	90/244 (37%)	164/240 (68%)	<.0001
All-treated:	90/244 (37%)	128/204 (63%)	<.0001

2.5.4.2.1 Secondary endpoints

Secondary endpoints analyzed included:

- Pain intensity
- Patient global assessment
- Investigator global assessment
- Patients achieving individually selected pain management goal
- Patients requiring rescue during the first three hours after system application.

As documented in Dr. McNeal's review, analyses of the secondary endpoints supported the conclusion of efficacy for E-TRANS. With respect to the need for rescue in the first three hours, in the all-treated population (which includes patients who dropped out of the study during the first three hours, primarily due to inadequacy of analgesia) more patients treated with placebo systems required rescue medication than patients treated with active E-TRANS (58% vs 46%, p = .0082). Among those subjects who completed the three-hour period during which rescue was available (the evaluable population) 45% of the E-TRANS group and 52% of the placebo group used rescue while it was available, but the difference was not statistically significant. This suggests that E-TRANS was providing some measure of analgesia during the first three hours, since fewer patients with an active system required the available rescue medication, and fewer dropped out during the first three hours, compared to patients with placebo systems. However, nearly half of E-TRANS treated patients felt the need for supplemental analgesia, implying that E-TRANS alone is unlikely to provide sufficient pain control in the immediate post-op period for a substantial fraction of patients.

The adherence of the E-TRANS system was also assessed. Approximately 90% of the systems were at least 90% adhered throughout treatment.

2.5.4.3 Technical Failures

Although technical failure was reported as a reason for discontinuation by only one patient in this study, multiple technical failures were reported. There were 17 reports of technical failures with E-TRANS fentanyl systems. ALZA's analysis showed

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

Technical failures, or suspected failures, affected 7% of the active systems and fully 18% of the placebo systems. Although these failures were primarily of a nature that prevented drug delivery, and are therefore not a major safety concern, they clearly represent an efficacy concern.

2.5.4.4 Efficacy Conclusion, Study C-95-016

This study has demonstrated efficacy of the E-TRANS fentanyl system in comparison to placebo for a single 24-hour application period in patients who have been successfully titrated to comfort with parenteral opioids prior to system application, and have been provided with access to i.v. rescue medication for the first three hours post surgery.

3 SAFETY

3.1 Exposure

The adverse event profile of fentanyl, including transdermal fentanyl, has been evaluated in the context of review of other fentanyl-containing products. In this application, the overall exposure to E-TRANS fentanyl at the proposed to-be-marketed dose and duration was adequate to characterize the safety profile of this syetem. The overall safety database includes 1935 individuals who were exposed to E-TRANS fentanyl and are included in the integrated safety database.

Both 40 μg and 25 μg doses were included in the integrated safety database, although the 25 μg system is not currently proposed for marketing. Most studies involving the40 μg sytem provided for a single application; therefore exposure to this dose is primarily for 24 hours or less. A dose-by-duration table is shown below (from Dr. McNeal's review)

E-TRANS fentanyl exposure by time interval

Time Interval	Total	40 mcg	25 mcg
Number of subjects	1907	1142	765
<3 hours	36	28 (2.5%)	8 (1%)
≥3-24 hours	744	564 (49.4%)	180 (23.5%)
>24-≤48 hours	854	319 (27.9%)	535 (69.9%)
>48-<72 hours	243	206 (18%)	37 (4.8%)
>72 hours	30	25 (2.2%)	5 (0.6%)

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.

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 (2.5%)	6.9 (0-13)
≥3-24 hours	564 (49.4%)	30.4 (0-88)
>24-≤48 hours	319 (27.9%)	38.7 (0-163)
>48-<72 hours	206 (18%)	71.8 (13-225)
>72 hours	25 (2.2%)	80.4 (23-208)

3.2 Deaths

No deaths occurred during treatment with an E-TRANS system. 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. All subjects had been treated with active systems.

Patient	Dose/duration	Circumstances of Death
Study C2000-006 Patient 110 83 yo F	25 μg	Died on POD #3 of presumed pulmonary embolism
Study C93-023 Patient 125 63 yo M	25 μg	Discharged uneventfully; rehospitalized 1 week later with chest pain/dyspnea; died of presumed pulmonary embolism
Study C-2001-011 Patient 1212 79 yo M	40 μg x 3 hrs d/c due to inadequate analgesia	POD #2 sudden death in setting of increasing oxygen requirements; presumed pulmonary embolism
study C-94-0 Patient 30235 64 yo M	40 μg x 72 hrs	Died of sepsis ~2wks post-op due to surgical complications
study C-94-058 Patient 30598 66 yo M	40 μg x 39 hrs d/c due to delirium ("became psychotic"	Died of sepsis and pneumonia in setting of ongoing mental status changes, ~4 wks post study participation

No deaths appear plausibly related to study drug; the absence of any deaths on placebo may be partially explained by the unequal randomization and the larger number of patients exposed to active drug (1935) vs placebo (321).

3.3 Discontinuations

There were relatively few discontinuations attributable to adverse events in the overall safety database. As shown in the table below, the rate of discontinuation due to AE was similar in the E-TRANS and placebo groups, and higher in the groups treated with morphine.

Reasons for Premature Discontinuation in E-TRANS Trials

	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%)**

Overall, 66 of 1958 patients treated with E-TRANS fentanyl discontinued due to adverse events (3%). This is similar to the discontinuation rate due to adverse events in the placebo population, and slightly lower than the rate (5%) in the population treated with i.v. morphine.

3.4 Serious Adverse Events

Dr. McNeal reviewed the CRFs for the SAEs occurring in the overall safety database and noted the following:

> 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, some of which 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

Other serious adverse events included several episodes of mental status changes, some of which were attributable to post-operative complications unrelated to study medication, and some of which may have been attributable to hypoxia, possibly drug-related. Events involving hypoventilation/hypoxemia were also reported, in both E-TRANS fentanyl and

i.v. morphine treated patients.

3.4.1 Thromboembolic Events

In addition to the three fatalities attributed to pulmonary emboli, noted above, six other cases of pulmonary embolus, one case of deep venous thrombosis, and one embolic stroke were noted. Of these, four occurred in patients treated with E-TRANS fentanyl and two occurred in patients treated with morphine PCA. These events are tabulated below.

E-TRANS fentanyl		Comparator	
C-2000-008 Patient 306 44 yo F	E-TRANS fentanyl x 24 hours; pulmonary embolus POD 2	C-94-058 Patient 30406 52 yo F	I.M. morphine x ~15 hours; pulmonary embolus POD 10
C-95-016 Patient 1032 47 yo F	E-TRANS fentanyl x 24 hours; pulmonary embolus ~2 weeks post-op	C-2000-007 Patient 116 68 yo F	I.V. morphine x 72 hours; pulmonary embolus @hour 55
C-95-016 Patient 1070 48 yo F	E-TRANS fentanyl x 24 hours; pulmonary embolus POD 2	C-2000-007 Patient 360 71 yo M	I.V. morphine PCA x 72 hours; DVT 1 day following study completion
C-94-059 Patient 30094 54 yo M	E-TRANS fentanyl; pulmonary embolus POD 3		
C-2000-007 Patient 2220 35 yo F	E-TRANS fentanyl x <24 hours; d/c due to decreased responsiveness not improved by d/c of Etrans system and administration of Narcan within 24 hr of surgery; dx embolic stroke POD 3		

Adjusting for the difference in the size of the exposed populations, there does not appear to be an enhancement in risk of thrombosis or pulmonary embolus when E-TRANS fentanyl is used in place of morphine for patient-controlled analgesia in the first 24 hours post-operatively. However, none of the 321 patients treated with E-TRANS placebo reported pulmonary embolus.

3.5 Common Adverse Events

Dr. McNeil pooled the data from subjects exposed to the 40μg E-TRANS fentanyl system. She noted that more of the patients who received E-TRANS fentanyl 40 μg

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. Nausea and vomiting are expected effects of fentanyl, while application site reaction is a common adverse event associated with the use of transdermal delivery systems. However, the description of these reactions suggests they may be of a more severe nature than encountered with typical, non-iontophoretic transdermal systems. Fever is also expected among post-operative patients; however, the higher rate of occurrence of fever in the active group compared to the placebo group is unexplained.

The likelihood of experiencing adverse events was also related to the amount of fentanyl administered. A maximum of 80 doses could be administered over the 24 hours of patch use, but the majority of patients used 60 or fewer of the available doses.

The table below (from Dr. McNeil's review) illustrates the most commonly reported adverse events in patients using the 40 μg E-TRANS fentanyl system, pooled across trials.

AE reported in >2% in all clinical studies of 40 mcg E-TRANS systems

	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 (17.5%)	*179 (17.4%)*	*21 (18.9%)*	34 (10.6%)
Headache	165 (14.4%)	*143 (13.9%)*	*22 (19.8%)*	21 (6.5%)
Abdominal Pain	66 (5.8%)	*58 (5.6%)*	*8 (7.2%)*	5 (1.6%)
Back pain	47 (4.1%)	*38 (3.7%)*	*9 (8.1%)*	11 (3.4%)
Pain	28 (2.5%)	*27 (2.6%)*	*1 (0.9%)*	3 (0.9%)
Cardiovascular				
Hypotension	33 (2.9%)	*31 (3.0%)*	*2 (1.8%)*	2 (0.6%)
Hypertension	27 (2.4%)	*25 (2.4%)*	*2 (1.8%)*	5 (1.6%)
Digestive				
Nausea	511 (44.7%)	*453 (44%)*	*57 (51.4%)*	81(25.2%)
Vomiting	198 (17.3%)	*177 (17.2%)*	*21 (18.9%)*	19 (5.9%)
Nausea and vomiting	35 (3.1%)	*30 (2.9%)*	*5 (4.9%)*	2(0.6%)
Constipation	28 (2.5%)	*24 (2.3%)*	*4 (3.6%)*	2(0.6%)
Hematologic				
Anemia	52 (4.6%)	*44 (4.3%)*	*8 (7.2%)*	3 (0.9%)
Nervous				
Dizziness	78 (6.8%)	*74 (7.2%)*	*4 (3.6%)*	4 (1.2%)
Insomnia	31 (2.7%)	*27 (2.6%)*	*4 (3.6%)*	17 (5.3%)
Hypertonia	25 (2.2%)	*17 (1.7%)*	*8 (7.2%)*	1 (0.3%)
Somnolence	22 (1.9%)	*19 (1.8%)*	*3 (2.7%)*	0
Anxiety	16 (1.4%)	*13 (1.3%)*	*3 (2.7%)*	6 (1.9%)
Respiratory				
Hypoxia	30 (2.6%)	*23 (2.2%)*	*7 (6.3%)*	2(0.6%)
Dermatologic system				
ASR**	206 (18%)			15 (5%)
Pruritis	89 (7.8%)	*72 (7%)*	*17 (15.3%)*	1 (0.3%)
Wound site bleeding	25 (2.2%)	*24 (2.3%)*	*1 (0.9%)*	2(0.6%)
Diaphoresis	17 (1.5%)	*14 (1.4%)*	*3 (2.7%)*	0
Urogenital system				
Urinary retention	41 (3.6%)	*32 (3.1%)*	*9 (8.1%)*	2(0.6%)

*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)

3.6 Adverse Events of Note

3.6.1 Application Site Reactions

In addition to collecting spontaneous reports of erythema, pruritis, or other local irritation at the application site, the protocols called for skin-site assessments to be 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. Erythema was graded on a scale from "none" to "beet redness." The table below illustrates that application site erythema was both more common and more severe among patients treated with the active patch than with the placebo patch.

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%)

In two patients, hyperpigmentation at the application site lasted two to three weeks. This finding was coded as application site reaction-postinflammatory. Three patients noted a 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."

Because the clinical studies involved primarily single applications of the E-TRANS system, many patients may have become aware of the application site reaction only upon discontinuation of system use. However, patient-controlled analgesia is not limited to the first 24 hours post-operatively, and multiple daily applications of the E-TRANS system may be anticipated. It is possible that the occurrence of these reactions may deter patients from continuing to use the E-TRANS system, and that longer studies might have detected a higher rate of dropout due to adverse event, with attendant impact on the overall risk/benefit assessment. The labeling should address the occurrence of application site reactions and should provide guidance, if available, concerning the placement of subsequent systems if skin irritation occurs in a multi-use setting.

3.6.2 Effects on Respiration and Oxygenation

One of the risks of fentanyl is respiratory depression or hypoxia. Information was collected in clinical studies on the occurrence of "Clinically Relevant Respiratory Depression" (CRRD), and on the oxygen saturation of study participants.

CRRD 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, CRRD 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.

No cases of CRRD were reported in patients using E-TRANS fentanyl. The only reported case of CRRD occurred on study C-2000-007, involving a patient who was receiving IV PCA morphine.

Oxygen saturation was monitored during the clinical trials, and the number of subjects experiencing desaturation (oxygen saturation <90%) was tabulated. As shown in the table below, subjects treated with E-TRANS fentanyl were more likely than patients treated with placebo to experience desaturation; however, fewer patients treated with E-TRANS fentanyl experience desaturation compared to patients treated with PCA morphine. Intramuscular morphine (not under patient control) was associated with the highest frequency of desaturation.

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	0.8%
E-TRANS Placebo	0.9%
E-TRANS fentanyl 40 mcg	**3.2%**
E-TRANS fentanyl 25/40 mcg	3.6%
IV PCA morphine	6.4%
IM morphine	9.3%

3.7 Clinical Laboratory Studies, ECGs

Clinical laboratory evaluations and ECG's were not included in the data collection for this product.

3.8 Safety Conclusions

The safety profile of E-TRANS fentanyl is consistent with the known safety profile of other fentanyl products. Particular attention in labeling should be given to application site reactions and to the need to ensure that only the patient administer doses from the E-TRANS fentanyl system, to prevent overdose and respiratory depression.

4 RISK MANAGEMENT CONCERNS

Risk management issues have been reviewed by the Controlled Substances Staff (HFD-009) and the Office of Drug Safety. The key concern related to E-TRANS fentanyl is the presence of a very large amount of drug even in used patches. The fentanyl gel can be easily removed from either new or used patches, and may be readily diverted. The need for witnessed disposal of used patches must be emphasized. Other recommendations on risk management are provided by consultant reviews.

5 PRODUCT QUALITY ISSUES

Product quality issues have plagued the development program for E-TRANS fentanyl, with "technical failures" causing premature termination of several studies. Technical failures were also noted in the pivotal efficacy trials submitted in support of this application. The nature of these failures was reviewed by the staff of the Center for Devices and Radiological Health, and by the HFD-170 CMC review team. It was concluded that the nature of the failures did not present a safety concern, in that all modes of failure result in non-functional systems which do not deliver drug. However, this represents a clear efficacy concern. Certain design features contributing to the [redacted] have been modified, and this particular technical failure is expected to be resolved. However, the design of the product [redacted] leading to non-functionality during the proposed period of expiration dating. The sponsor anticipates that a maximum of [redacted] of the systems will be non-functional by the end of the expiry period. A solution has been proposed, involving labeling the product to require a functionality test by the pharmacist and/or health care provider prior to removing the product from the patch. While the nature of the functionality test requires clarification and may not be unduly burdensome, the sponsor has not fully delineated what action can practically be taken to secure, dispose of, and/or obtain reimbursement for non-functional patches. With the possibility of [redacted] of the systems failing the functionality test, this is an essential aspect of risk management for this product.

6 CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS ISSUES

As documented in Dr. Nallani's review, the attainment of maximal blood levels after dose delivery is notably less rapid from the E-TRANS system in comparison to intravenous delivery. Furthermore, the initial doses delivered from the system are lower than the labeled per-dose amount by roughly 25%. A period of equilibration is required before the full labeled dose is delivered; this appears to occur after approximately 20 doses. This phenomenon may partially explain the need for i.v. rescue during the initial three hours of wear: a very substantial minority of patients using E-TRANS fentanyl required i.v. rescue during the first three hours of system use (up to 45%). Although the pharmacokinetics of multiple day dosing have been studied, these studies employed regular, every-10-minute, dosing which does not simulate the clinical situation in which patients are likely to have prolonged intervals when no doses are administered (e.g.,

during sleep). If re-equilibration of the patch is required to attain sufficient dosing after a period of no dosing, or if a new patch must equilibrate anew if applied after a period without dosing, patients will not receive adequate pain relief during these periods of re-equilibration. No study analyzed for efficacy involved more than a single application of the E-TRANS system.

According to information provided by Alza in a teleconference on June 30, 2004, equilibration of the system and attainment of full delivery does not require repeated activation of the system. Alza indicated that mere contact with the skin for a period of three hours would be sufficient to ensure delivery of the labeled dose, even if the system were not activated. However, studies purporting to support this assertion were evaluated by Dr. Nallani, who noted that blood levels were not assessed at the end of three hours. No data between hour 1 and hour 12 were collected. Therefore, it cannot be assumed that the E-TRANS system will deliver the labeled, effective dose after three hours of passive contact with the skin. However, PK data supplied by Alza did suggest that re-equilibration after sleep or after system change is unlikely to require an additional three-hour period of access to i.v. rescue.

7 CONCLUSION AND RECOMMENDATIONS

This application contains substantial evidence of efficacy of E-TRANS fentanyl system as a patient-controlled analgesic in a very specific setting: post-operative patients who received a single 24-hour application period after being successfully titrated to comfort with parenteral opioids prior to system application, and who were provided with access to i.v. rescue medication for the first three hours post surgery; notably, a substantial fraction of patients took advantage of the availability of i.v. rescue. The safety profile has been adequately characterized and no specific safety concerns related to the dosage form were identified.

However, significant concerns exist regarding the practical application of the product in clinical use. It is not clear how i.v. rescue will be made available to patients during the initial three hours of system use. It may be necessary for the patient to activate the device repeatedly in order to attain the full, labeled, apparently effective dose. If two forms of patient-controlled analgesia are supplied (E-TRANS fentanyl and intravenous PCA rescue), it is not clear how the patient will be instructed to administer drug. If the intravenous "rescue" is to be available by request from a nurse, it is unlikely the patient will have access to pain relief in a timely fashion if it is necessary to wait 10 minutes after E-TRANS system activation before requesting rescue. Practically speaking, if intravenous analgesia is needed during the first three hours, there seems to be little role for the iontophoretic system during that time; however, if the system goes unused during the first three hours, it is not known whether the necessary equilibration will occur and the system may be ineffective even after i.v. analgesia is no longer available. If passive contact is all that is necessary, the system could potentially be placed before or during surgery, to provide equilibration time. However, the use of the product in this manner was not studied and the available data are insufficient to support this recommendation.

Another very significant concern is the potential for diversion and misuse of the fentanyl gel contained in both used and unused patches. Product quality issues predicting a rate of non-functional patches approaching — at the end of the expiry period further accentuate this concern, as these non-functional systems will create further opportunity for misuse. Alza's approach to management of non-functional systems is incompletely delineated at this time, and further product design improvements intended to significantly decrease the rate of product failure are identified but have not yet been implemented. A functionality test has been proposed, but may address only some types of product failures.

It is recommended that approval be withheld until the sponsor clearly addresses the practical issues related to the use of the product; which raise concerns of efficacy (if each system delivers inadequate doses for the first several hours of use), safety (due to uncertainty of how and when to deliver i.v. rescue during the period of system equilibration), and abuse and diversion; and until design improvements have been implemented and the rate of product failure has been substantially reduced.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Celia Winchell
5/10/2006 06:52:42 PM
MEDICAL OFFICER
Date of review: July 15, 2004; entered late into DFS.

CLINICAL REVIEW

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthetic, Critical Care, and Addiction Drug Products
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857
Tel: (301) 827-7410

Medical Officer Review

Date of Submission:	**September 23, 2003**
Type of Submission:	**New Drug Application 21-338**
Product:	**E-TRANS (fentanyl HCL) Patient Controlled transdermal system**
Sponsor:	**ALZA**
Review Date:	**June 17, 2004**
Medical Officer:	**Dawn Elizabeth McNeil, M.D.**
Project Manager:	**Kimberly Compton**

Table of Contents

Table of Contents 2

Executive Summary 5

I. **Recommendations** 5

A. Recommendation on Approvability 5

B. Recommendation on Phase 4 Studies and/or Risk Management Steps 6

II. **Summary of Clinical Findings** 7

A. Brief Overview of Clinical Program 7

B. Efficacy 7

C. Safety 8

D. Dosing 10

E. Special Populations 10

Clinical Review 12

I. **Introduction and Background** 12

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups 12

B. State of Armamentarium for Indication(s) 13

C. Important Milestones in Product Development 13

D. Other Relevant Information 15

E. Important Issues with Pharmacologically Related Agents 15

II. **Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews** 15

III. **Human Pharmacokinetics** 19

IV. Description of Clinical Data and Sources 21

A. Overall Data 21

B. Table Listing the Clinical Trials 24

C. Postmarketing Experience 25

D. Literature Review 25

V. Clinical Review Methods 25

A. How the Review was Conducted 25

B. Overview of Materials Consulted in Review 25

C. Overview of Methods Used to Evaluate Data Quality and Integrity 25

D. Were Trials Conducted in Accordance with Accepted Ethical Standards. 25

E. Evaluation of Financial Disclosure 26

VI. Integrated Review of Efficacy 27

A. Brief Statement of Conclusions 27

B. General Approach to Review of the Efficacy of the Drug 28

C. Detailed Review of Trials by Indication 30

C-95-016 30

C-2000-008 42

C-2001-011 54

C-2000-007 65

D. Efficacy Conclusions 71

VII. Integrated Review of Safety 73

A. Brief Statement of Conclusions 73

B. Description of Patient Exposure 74

C. Methods and Specific Findings of Safety Review 77

D. Adequacy of Safety Testing 86

E. Summary of Critical Safety Findings and Limitations of Data 86

VIII. Dosing, Regimen, and Administration Issues 87

IX. Use in Special Populations 89

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation 89

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy 89

C. Evaluation of Pediatric Program 90

D. Comments on Data Available or Needed in Other Populations 91

X. Risk management plan 92

XI. Conclusions and Recommendations 93

A. Conclusions 93

B. Recommendations 96

XII. Appendices 97

A. ASA classifications 97

B. Individual Detailed Study Descriptions 98

C. Patients who discontinued for adverse events 139

D. Patients who discontinued due to adverse events in studies of 48 or 72 hour duration 143

Clinical Review for NDA 21-338

Executive Summary

I. Recommendations

A. Recommendation on Approvability

I recommend an approvable action for this product pending resolution of the outstanding device mechanism, device failure rate and clinical feasibility issues.

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 apparent period of skin equilibration.

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. Patients must have intravenous rescue medication available to them for the first three hours that the system is in place. The sponsor has not addressed the clinical feasibility of expecting patients to activate the E-TRANS device then wait before activating the IV PCA. I would think that most patients, if they were to realize that the E-TRANS device was not providing relief as quickly as the intravenous medication was, would activate the IV PCA instead of the E-TRANS device at the onset of pain. The E-TRANS device must be activated 18-20 times before it may be expected to deliver doses of approximately 40 mcg. If the patients are not to be given an IV PCA, but rather to be dependent upon the nurses providing IV rescue medications, this may impose unnecessary suffering as the patient will have to wait for the nurse's availability to deliver the necessary analgesia.

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.

While the safety testing done for the drug moiety, fentanyl, was adequate, further characterization of the device failure rate is important. At the present time, we are told that the "out of the box" failure rate may be expected to be 0% at 6 months and 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.

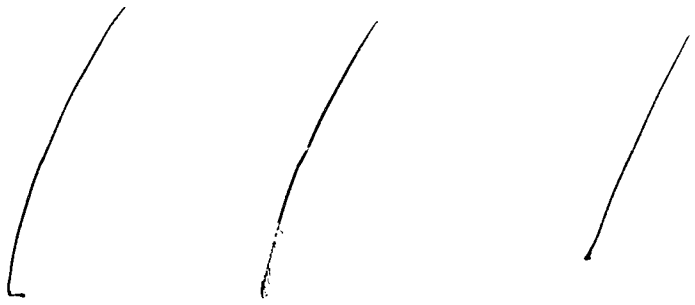
It may be expected that there will be a certain amount of device misuse e.g., persons other than the patient administering the on-demand dosing. If the patient were to be the only one administering on-demand doses, he/she would stop administering the doses if he/she were to become somnolent due to the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

The device aspects of E-TRANS were evaluated by reviewers in CDRH. Although according to that review malfunctioning devices provided no drug and therefore did not expose the patient to risk of possible overdose, questions remain about the device mechanisms. The accurate functioning of the device is integral to the safety assessment for this product so it is essential that all questions about the device's function be answered prior to approval of E-TRANS for marketing.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

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.

The risk management plan includes



II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

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. The device is comprised of two layers. The top contains the 3 volt lithium battery and other electronic components. The bottom contains the skin adhesive and two hydrogel reservoirs: an anode containing fentanyl hydrochloride; a cathode containing pharmacologically inactive materials.

E-TRANS permits patient controlled transdermal administration of 40 mcg of fentanyl. This 40 mcg fixed-dose is delivered, with a dosing duration of 10 minutes, when the button on top of the system is depressed twice within 3 seconds. The patient may administer a dose every 10 minutes but may administer no more than 80 doses. The device ceases to function 24 hours after the first dose or after 80 doses have been administered, whichever occurs first.

This submission includes 28 studies, 4 of which were controlled safety and efficacy studies. ALZA performed three placebo-controlled trials in support of efficacy, as well as one active controlled trial. Six studies were terminated early due to technical difficulties. Overall, 2660 patients participated in these studies, 1142 of whom received the E-TRANS 40 mcg system which is the subject of this submission. The remainder received the 25 mcg E-TRANS system, a placebo or an active control.

Additionally, 5 pharmacology studies were performed in healthy volunteers using an early version of the E-TRANS system, 5 wearing studies were performed which used placebo E-TRANS systems and a dose-ranging study was performed using IV PCA fentanyl.

B. Efficacy

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.

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. It should be noted that after about the 40^{th} dose, the device delivers, *in vivo*, about 44 mcg per dose, a 10% increase over the nominal dose.

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.

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.

C. Safety

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

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.

While five patients died after completing or withdrawing from the study, no study site reported a patient dying while an E-TRANS system was in place.

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. As an opiate, fentanyl 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 reports of pulmonary embolism; one report of embolic stroke. No reports of embolic events were reported in the placebo population. It is difficult to fully evaluate the significance of this finding since we do not know the background rate of post-operative embolic events. However, since no cases of pulmonary embolism 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.

In one patient, whose past medical history was notable for chronic obstructive pulmonary disease and tobacco use, atelectasis and hypoxemia were noted during use of E-TRANS. It is unclear whether mild opiate-induced respiratory depression may have contributed to atelectesis in a patient with insufficient pulmonary reserves. Use of E-TRANS fentanyl or other potent opiates 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%. 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, approximately 60% of patients noted erythema and/or pruritis at the E-TRANS application site.

D. Dosing

A multi-center, randomized, double-blind, parallel group dose-ranging study was done 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). 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 of the maximum opioid requirements in patients treated for postoperative pain revealed that 80 doses of 40 mcg appeared sufficient to treat most patients.

E-TRANS was designed to provide a ten minute dosing interval, minimizing local skin irritation from iontophoretic delivery of 40 mcg fentanyl.

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

E. Special Populations

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.

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%).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.

The majority of the participants in these studies were Caucasian (79.2%). The White patients who received an opiate (fentanyl, or morphine) reported a higher incidence of adverse events than the Black patients 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 degrees of erythema may be difficult to discern in persons of darker skin pigmentation.

Assessments of AUC_{inf} done in Study 94-060 demonstrated no significant differences in AUC_{inf} between lean and obese individuals, an assessment done due to the lipophilic nature of fentanyl.

The pharmacokinetics of E-TRANS fentanyl in patients with hepatic impairment were not evaluated in support of this submission. However, fentanyl is metabolized by the cytochrome P450 (CYP) 3A4 system of the liver. Inhibitors of this system may be expected to decrease the systemic clearance of fentanyl and may enhance opioid effects. 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 (4.2%) of the 1142 patients who used E-TRANS fentanyl had an SAE, 7 of those patients (15%) were in the subpopulation of patients with probable renal or hepatic impairment. Overall 13(3.6%) of the 361 patients who used IV PCA morphine had an SAE, 1 of those patients (8%) 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.

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

E-TRANS (fentanyl HCL) patient-controlled transdermal system is the drug established name. ALZA has not yet determined a tradename for this product. The product will be referred to as "E-TRANS" throughout this review.

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. The device is comprised of two layers. The top contains the 3 volt lithium battery and other electronic components. The bottom contains the skin adhesive and two hydrogel reservoirs: an anode containing fentanyl hydrochloride; a cathode containing pharmacologically inactive materials.

E-TRANS permits patient controlled transdermal administration of 40 mcg of fentanyl. This 40 mcg fixed-dose is delivered, with a dosing duration of 10 minutes, when the button on top of the system is depressed twice within 3 seconds. The patient may administer a dose every 10 minutes but may administer no more than 80 doses. The device ceases to function 24 hours after the first dose or after 80 doses have been administered, whichever occurs first.

The E-TRANS system, between dose intervals, automatically flashes a light pulse code to indicate the approximate number of doses delivered. Each one-second light pulse represents up to five doses of fentanyl. To calculate the maximum number of doses which have been delivered, the observer would multiply the number of light pulses by five. If the observer should want to obtain this information during the 10 minute dosing interval, when the light is normally steady, it can be obtained by pressing the button once.

This iontophoretic system delivers fentanyl. As a synthetic phenylpiperidine opioid agonist, fentanyl may be expected to cause the following systemic effects: analgesia, respiratory depression, emetic effects with or without accompanying nausea, antitussive effects, decreased peristalsis and transient hyperglycemia. Opioids have distinct effects on the central nervous system and may cause miosis, increased parasympathetic activity and/or sedation. The common side effects of fentanyl include nausea, vomiting, constipation, somnolence, and diaphoresis. The most serious risk is respiratory depression.

ALZA's proposed labeling limits use of the E-TRANS system to adults with acute pain in [redacted]. The system is to be placed either on the chest or upper arm. Only one system is to be worn at a time. If consecutive systems are used, application sites should be rotated.

B. State of Armamentarium for Indication(s)

Fentanyl is currently available in the USA as an injectable solution, as a transdermal patch, and as an oral lozenge. Non-steroidal anti-inflammatory drug products and opioids such as morphine are used in patients utilizing patient controlled analgesia (PCA).

C. Important Milestones in Product Development

January 27 1993
The IND for Fentanyl Electrotransport System was filed.

April 1996
A closed meeting of the ALSDAC was held to discuss the development plan for E-TRANS as well as proprietary information on the mechanics of the device, including the electrophysiological tests done to provide consistent drug delivery. The information provided was deemed adequate.

February 18 1999
An End of Phase 2 meeting was held.
The following agreements were made:

- Two AWC studies were needed to provide basis for the claim of pain control in the acute postoperative setting
- [redacted]
- Population PK data would be obtained from one US study involving approximately 300 patients.
- The overall safety database of 2000 patients , including [redacted] , and 75-95 patients over 65 years, appeared acceptable.

April 28 1999
This advice meeting was called to clarify CMC issues for E-TRANS fentanyl.
At this meeting, Dr. Rappaport clarified the following points from the February 1999 meeting:

- The indication for this product sought is ' [redacted]
- The intent of the blood sampling in the US studies was for documentation of fentanyl delivery and not for population PK analysis.

January 18, 2001
A pre-NDA meeting was held with ALZA.
The following comments were made:

- Data on the safety of maximal exposure to the 40 mcg dose should be provided.

- The Division had "no concerns related to the waiver request for children under 6 years."
- ALZA was told that the following device related issues had to be addressed at the time of NDA submission:
  - Demonstration that the device remains reliable throughout its shelf life e.g. shuts off properly after administration of a single dose, after administering 6 doses in an hour and after administration of 80 doses
  - Demonstration of a 0% failure rate for the critical performance parameters of the device, e.g. delivery of the correct amount of fentanyl
- [redacted]
- A risk management plan was to be submitted, including special instructions for the physician, patient, advertising and promotion.

February 6 2001
The Division sent an advice letter stating that [redacted] You may wish to consider continuing with the development of the 40 mcg [redacted] restricted to the hospital setting where the opioid naïve post-operative patient can be adequately monitored."

May 12, 2001
ALZA submitted a response to the minutes from the January 18 2001 meeting.
The following changes were requested and clarifications were made:

- Device label and device manuals were not to be provided since E-TRANS was determined to be a drug product.
- The Division was told that a pharmacokinetic study would be planned to determine the result of patients receiving the maximal amount of doses (n=80) in the minimum amount of time (13.33 hours).

[redacted]

June 6 2001
A Type A meeting was held with ALZA.

1. The division indicated that the major obstacles to ALZA's current development plan for E-TRANS were 1) [redacted] and 2) need for safety data on the higher and maximum number of 40 mcg dose activations.
2. ALZA indicated that in PCA systems safety is the sum of the safety of the delivery system, the drug delivered and the patient experience of pain...ALZA's current safety database indicates that the number of subjects using more than 70 activations represent only 5% of the total population investigated. ALZA proposed studying the safety of using the higher and maximum number of activations as a post-marketing commitment.
3. ALZA indicated that their intention is to launch the 40 mcg dose in a medically supervised setting. The Division indicated that this setting would help to provide adequate safety monitoring and the review of the application would determine the adequacy of the safety of the product using the higher or maximum number of doses.
4. A risk management program was to be implemented at the time of the NDA approval. It should include [redacted]
5. [redacted]

D. Other Relevant Information

This product is not approved for use in any market, domestic or foreign.

E. Important Issues with Pharmacologically Related Agents

Drug-drug interactions have been identified with inhibitors of cytochrome P450 and/or isoenzyme 3A4.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

CMC

A CMC review has been performed by Dr. Rajiv Aggarwal. The CMC team leader for HFD-170, Dr. Ravi Harapanhalli, as well as a device inspector, Mr. Mark Chan, went to inspect the sponsor site in May 2004. A review of the design control procedures and documents/records associated with the E-TRANS (fentanyl HCL) System revealed that the firm has adequately implemented appropriate procedures for the design and development of the THA (Top Housing Assembly). During this inspection the design and development documents for the THA were reviewed. The design and development plan was provided.

During the clinical trials, the early systems were found to have technical failures. These technical failures have been addressed through both changes in the system components and changes in the testing procedures. The modified systems, the so-called "corrective action lots," are currently being evaluated for stability. The currently available data indicates that we may grant a shelf life of [redacted] or the corrective action lot with a expectation of a zero defect rate.

Biopharmaceutics

A biopharmaceutics review has been performed by Dr. Srikanth Nallani.
I will summarize the main clinically relevant finding from his review. 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. The sponsor maintains that it is not the number of activations but rather the duration of wear that allows skin equilibration and subsequent delivery of the nominal dose of 40 mcg/activation. The studies performed do not adequately address this issue since in all cases the patients activated the system (albeit to varying degrees) during the three hour skin equilibration period.

Statistics

A statistical review has been performed by Dr. Milton Fan in the Division of Biometrics II. Although his review is on file, I will summarize his key findings here. In short, Study C-95-016 demonstrated that E-TRANS was superior to placebo. This finding was replicated in Study C-2001-011.

Study 2001-011:

Dr. Fan's analysis of the primary endpoint was consistent with the sponsor's findings. He performed a subgroup analysis which demonstrated a treatment difference in favor of E-TRANS fentanyl which was consistent across center, gender and age. There was a statistically significant difference in the percentage of patients who required rescue medication, with those patients who received active drug requiring less rescue medication than those who received placebo. A disproportionate number of suspected technical failures was noted, with more than twice as many in the placebo group (n=42) as opposed to the fentanyl group (n=17), p=0.0015.

Study C-2000-008:

Dr. Fan's analysis of the primary endpoint was only partially consistent with the sponsor's findings. The finding for evaluable patients was only marginally statistically significant with a p-value of 0.05. The finding for all treated patients was not statistically significant with a p-value of 0.07. He performed a subgroup analysis which demonstrated an inconsistent treatment difference in favor of E-TRANS fentanyl which was consistent

across center, gender and age. The percentage of patients who dropped out for any reason was statistically significant biased in favor of the active treatment group. There was no statistically significant difference between the two groups in the secondary endpoints of patient global assessment or use of rescue medication. When mean pain intensity scores were reviewed, there was no treatment difference found at Hour 24, p-value 0.85. When change from baseline to Hour 24 in all treated patients was evaluated, there was no treatment difference, p-value 0.32.

Study C-95-016:
Dr. Fan's analyses of the primary and secondary endpoints were consistent with the sponsor's findings. No subgroup analysis was performed as the sample size for the placebo group was insufficient.

Center for Devices and Radiological Health (CDRH)
CDRH
A detailed review of the iontophoretic device has been performed by Dr. Kevin Lee in the Center for Devices and Radiological Health (CDRH). His review is on file so I will only summarize the key deficiencies found.

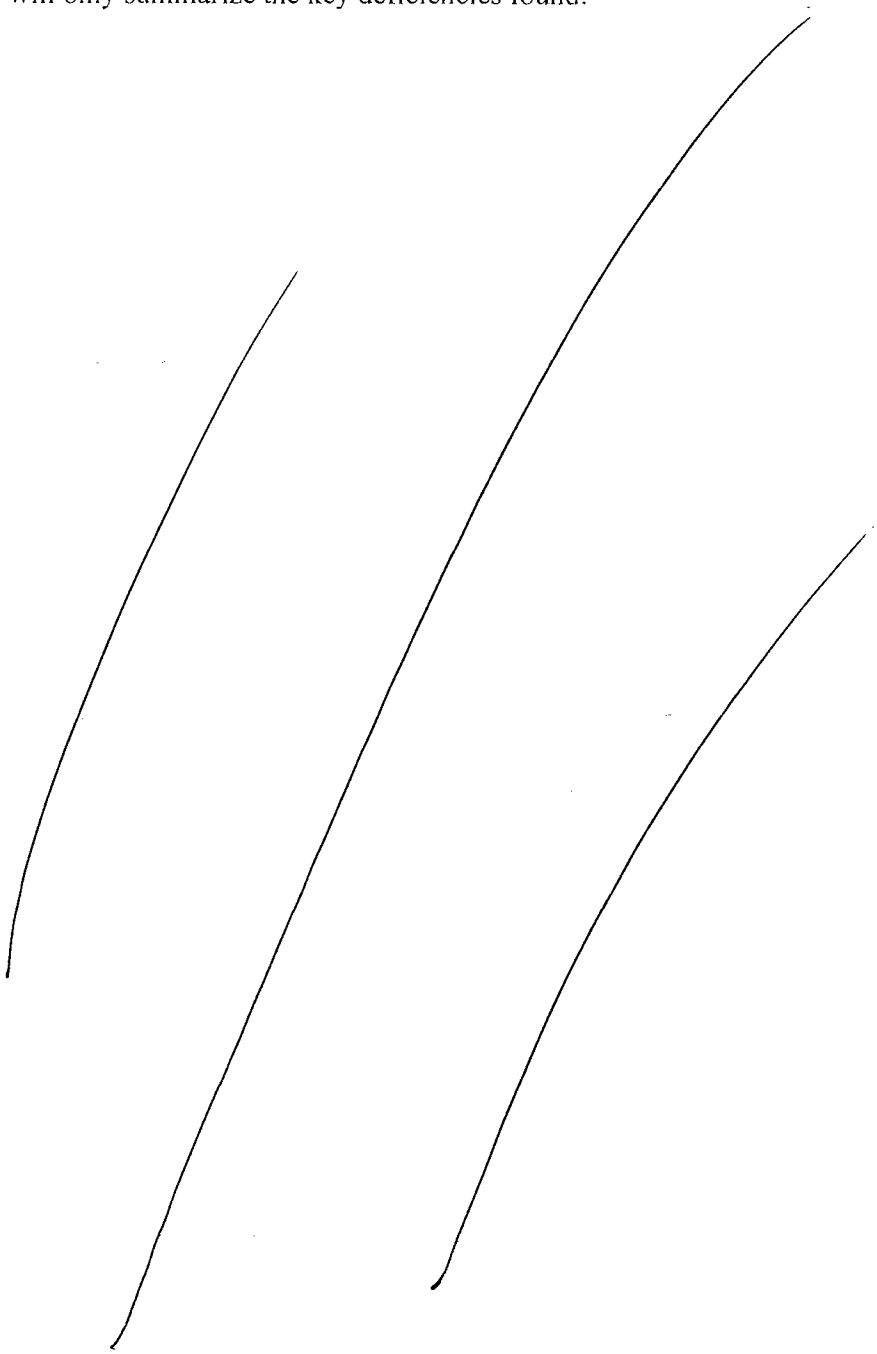
Dr. Lee stated that he had no safety concerns, though he notes that — of the devices that underwent stability testing failed to activate a current when tested at — He notes detailed descriptions of the device components were not included in the NDA. He requested that Sponsor address the following specific deficiencies:

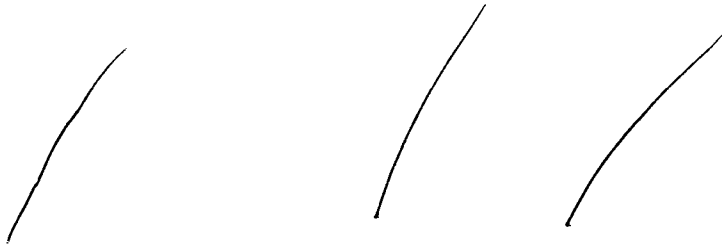
1. Explain the mechanism your device uses to maintain and regulate current, voltage, and —
2. Explain how the individual components of your device, such as —, integral circuit, etc. work together.
3. Describe the mechanism for delivering exactly 80 doses to the patients
4. Describe how the — maintains each dose for 10 minutes
5. Describe the — in your device
6. Describe the accuracy of the —
7. Describe how the — aintains the current and voltage for 10 minutes in your device
8. Provide data from the — corrective action lots for the problem when these are available

Reviewer's note: Although Dr. Lee stated that malfunctioning devices provided no drug and therefore did not expose patients to risk of possible overdose, questions remain about the actual device mechanism as may be seen from his list of specific deficiencies. The accurate functioning of the device is integral to the safety assessment for this product.

CDRH/OC
A detailed review of the iontophoretic device was been performed by Dr. Carol Arras in the Center for Devices and Radiological Health (CDRH, Office of Compliance). She reported being concerned about the number of design changes that have been made or are in the process of being made for the E-TRANS Fentanyl Delivery System, suggesting

that adequate design validation has not been completed for this product. Each of the changes would require associated validation and verification activities. Her review is on file so I will only summarize the key deficiencies found:





III. Human Pharmacokinetics

Fentanyl is a highly lipophilic synthetic opioid agonist that interacts primarily with μ-receptors distributed in the brain and spinal cord as well as other tissues. Clinically the principal effects are referable to the central nervous system, where it produces analgesia, sedation and/or drowsiness. While major cardiovascular effects are not usually seen, orthostatic hypotension and syncope have been reported. The effects on urinary smooth muscle are variable with complaints of urinary frequency and urgency both having been reported.

The primary metabolic pathway for fentanyl is the human cytochrome P450 3A4 isoenzyme system. Fentanyl is metabolized through oxidative N-dealkylation to inactive metabolites. Studies done after intravenous administration of fentanyl show predominantly renal excretion of metabolites with less than 10% of the original dose found in fecal matter.

Ten pharmacokinetic studies were done in adults to support the use of 40 mcg on-demand dosing in acute pain (C-92-038, C-93-019, C-94-060, C-94-067, C-94-068, C-96-009, C-97-001, C-98-013, C-2001-009, C-2002-027). Five studies were presented as additional supportive evidence (C-90-049, C-91-001, C-92-029, C-94-055, C-95-032). Much of the text below describing the results of these studies is taken from ALZA's summary of pharmacokinetics.

Fentanyl is rapidly distributed after an IV bolus with greater than 80% of the dose leaving the plasma in under 5 minutes and 98.6% of the dose leaving the plasma within 60 minutes. Elimination is through redistribution into muscle and fat, which they act as storage depot releasing fentanyl slowly back into systemic circulation. Fentanyl is approximately 84.4% protein bound at physiological pH, and a maximum of 90% is bound occurs at pH 7.6. While patients at the extremes of age have increased protein binding, gender is not correlated with increased or decreased protein binding.

Fentanyl is hepatically metabolized to norfentanyl. Hydroxylation of norfentanyl and fentanyl lead to hydroxypropionyl norfentanyl and hydroxypropionyl fentanyl. Additional minor metabolites are produced through fentanyl amide hydrolysis, alkyl

hydroxlation and N-dealkylation. The pharmacological activity of all of the fentanyl metabolites is believed to be minimal.

Bioavailability of fentanyl after oral administration is 32%, while after oral-transmucosal administration, which bypasses first-pass metabolism, bioavailability increases to 52%. Using transdermal administration, 92% of the fentanyl dose reaches the systemic circulation unchanged.

Elimination of fentanyl is affected by re-uptake from storage depots such as fat and muscle as well as hepatic metabolism. Following an intravenous bolus, the half-life of fentanyl is 4-8 hours. When fentanyl is administered transdermally through a non-iontophoretic system, the elimination half-life after removal of the transdermal fentanyl system is 12-25 hours due to the slow release of the stored fentanyl in the skin under the system.

Mean C_{max} values were highest when E-TRANS fentanyl was applied to the upper outer arm or the chest. The lowest mean C_{max} values were seen when the system was worn on the lower inner arm, values were approximately 20% less than when worn on the upper outer arm or the chest. Study C-2002-007 demonstrated that passive delivery of the fentanyl from the E-TRANS system while not activated is present with a mean fentanyl absorption rate of 2.3 micrograms/hour.

No statistically significant AUC_{inf} differences were found during an analysis by demographic factors which considered the following variables: race (black, white); age (18-45 years, >65 years); weight (lean, obese); gender. Although the findings are not consistent, clearance is thought to be lower in the elderly. Studies of drug-drug interactions involving E-TRANS fentanyl were not performed. The pharmacokinetics of E-TRANS fentanyl in patients with hepatic or renal insufficiency have not been evaluated.

Table 1:
AUC evaluated by demographic factors

Statistical Summary of E-TRANS® Fentanyl AUCinf by Demographic Factors* in Study C-94-060

Level	LS Mean (SE)	n	Difference (SE)	p-value	95% CI (lower, upper)
Race					
Black	3.15 (0.303)	27	0.645 (0.517)	0.218	(-3.927, 1.6824)
White	2.50 (0.360)	36			
Age					
18-45 yrs	2.90 (0.253)	38	1.44 (0.488)	0.769	(-0.8359, 1.1244)
> 65 yrs	2.75 (0.378)	25			
Weight					
Lean	2.98 (0.326)	30	0.313 (0.424)	0.463	(-0.5378, 1.1648)
Obese	2.67 (0.267)	33			
Gender					
Female	2.71 (0.344)	26	-0.236 (0.525)	0.655	(-1.2902, 0.8182)
Male	2.94 (0.328)	37			

*Excluding subject 3011

Source: C-94-060 Final Report, Table 11.3.2

IV. Description of Clinical Data and Sources

A. Overall Data

This submission includes 28 studies, 4 of which were controlled safety and efficacy studies. Six studies were terminated early due to technical difficulties. Overall, 2660 patients participated in these studies, 1142 of whom received the E-TRANS 40 mcg system which is the subject of this submission. The remainder received the 25 mcg E-TRANS system, a placebo or an active control.

Additionally, 5 pharmacology studies were performed in healthy volunteers using an early version of the E-TRANS system, 5 wearing studies were performed which used placebo E-TRANS systems and a dose-ranging study was performed using IV PCA fentanyl. The safety information from these studies was not pooled into the safety database (ISS p.150).

The four studies done in support of efficacy will be detailed in Section VI of this review, Integrated Review of Efficacy. The studies that did not contribute to efficacy but did contribute to the safety database are briefly described below with detailed descriptions provided in appendix B. The pharmacokinetic results have been previously discussed in section III, Human Pharmacokinetics and Pharmacodynamics.

Placebo-controlled studies (Pivotal)

C-95-016 was a single-center, double-blind, placebo-controlled, parallel-group trial to evaluate the safety and efficacy of E-TRANS fentanyl (40 mcg on demand) for the management of postoperative pain in the first 24 hours after surgery.

C-2000-008 was a multi-center, randomized, double-blind, placebo-controlled, parallel-group trial to evaluate the safety and efficacy of E-TRANS fentanyl (40 mcg on demand) versus E-TRANS fentanyl (placebo) for the management of postoperative pain in the first 24 hours after surgery.

C-2001-011 was a multi-center, randomized, double-blind, placebo-controlled, parallel-group trial to evaluate the safety and efficacy of E-TRANS fentanyl (40 mcg on demand) for the management of postoperative pain in the first 24 hours after surgery. This study incorporated JCAHO Pain Management Standards.

Active comparator controlled studies (Pivotal)

C-2000-007 was a multi-center, randomized, open-label, active-controlled, parallel group single treatment trial to compare the safety and efficacy of E-TRANS fentanyl (40 mcg on demand) to IV PCA morphine for the management of postoperative pain in adults.

Uncontrolled safety and efficacy studies

C-93-023 was an open-label, single center, two part pilot study in which postoperative pain patients received up to 6 doses of 25 mcg on demand during part I and up to 6 doses of 40 mcg on demand during part 2.

C-94-043 was a single-center open-label follow-up trial for C-93-023 to determine whether the prescribed regimen of up to six 40 mcg on-demand doses per hour provides safe and effective management of postoperative pain on Days 2 and 3 after surgery.

C-95-019 was a multi-center open-label single treatment trial to evaluate the safety and efficacy of E-TRANS fentanyl (40 mcg on demand) for the management of postoperative pain after short stay surgical procedures.

C-96-020 was a single-center open-label single treatment trial to evaluate the safety and efficacy of E-TRANS fentanyl (25 mcg on demand) for the management of postoperative pain after short stay surgical procedures.

C-2000-005 was a multi-center open-label single treatment trial to evaluate the safety and efficacy of E-TRANS fentanyl (25 mcg on demand and 40mcg on demand) for the management of postoperative pain in pediatric patients.

C-2000-006 was a multi-center open-label single treatment trial to evaluate the safety and efficacy of E-TRANS fentanyl (25 mcg on demand) for the management of postoperative pain in elderly patients.

C-2000-009 was a multi-center open-label single treatment trial to evaluate the safety and efficacy of E-TRANS fentanyl (25 mcg on demand) for the management of postoperative pain after short stay surgical procedures.

Wearing studies using placebo E-TRANS systems

C-95-034 was a single-center randomized, open-label two-phase study to optimize the configurations for aspects of the circuitry, printed board-to-lower housing interface connection and skin adhesive for the E-TRANS commercial product and to evaluate the recommended sites for system application.

C-95-050 was a single-center randomized, open-label study to evaluate the effect of alcohol pretreatment of the skin on the time to achieve electrical compliance.

C-95-051 was a single-center randomized, open-label study to determine the optimal adhesive for the E-TRANS system.

C-95-053 was a single-center, open-label study to determine the optimal adhesive for the E-TRANS system.

C-96-003 was a single-center, open-label, single-treatment study to determine the difficulty of removing the E-TRANS system after 24 hours of wear. This study enrolled elderly and young adult healthy volunteers.

Additional studies :
FEN-INT-006 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 of fentanyl at 20 mcg, 40 mcg, and 60 mcg.

Studies which were stopped prematurely due to technical problems with the E-TRANS system
C-94-057 was a multi-center, randomized, open-label, active-controlled, parallel group single treatment trial to compare the safety and efficacy of E-TRANS fentanyl (40 mcg on demand) to IV PCA morphine for the management of postoperative pain in adults. This trial was terminated due to technical failures of the E-TRANS system.

C-94-058 was a multi-center, randomized, open-label, active-controlled, parallel group single treatment trial to compare the safety and efficacy of E-TRANS fentanyl (40 mcg on demand) to IM morphine for the management of postoperative pain in adults. This trial was terminated due to technical failures of the E-TRANS system.

C-94-059 was a multi-center randomized, double-blind, placebo-controlled, parallel group single treatment trial to evaluate the safety and efficacy of E-TRANS fentanyl (40 mcg on demand) for the management of postoperative pain in adults. This trial was terminated due to technical failures of the E-TRANS system.

C-96-055 was a multi-center open-label single treatment trial to evaluate the safety and efficacy of E-TRANS fentanyl (25 mcg on demand) for the management of postoperative pain after short stay surgical procedures. This trial was terminated due to technical failures of the E-TRANS system.

C-96-056 was a single-center open-label single treatment trial to evaluate the safety and efficacy of E-TRANS fentanyl (25 mcg on demand) in elderly patients. This trial was terminated due to technical failures of the E-TRANS system.

B. Table Listing the Clinical Trials

The pivotal trials are in **bold** font. The trials that were stopped prematurely are in *italic* font. Brief descriptions of the trials were given above. Detailed descriptions of the trials that were not evaluated for efficacy may be found in Appendix B.

Table 2:
Listing of clinical trials

Trial name	Number of patients randomized	Study duration	Data[a]
C-95-016	102 patients: 77 active, 25 placebo	24 hours	S,E
C-2000-008	205 patients:154 active, 51 placebo	24 hours	S,E
C-2001-011	484 patients: 244 active, 240 placebo	24 hours	S,E
C-2000-007	636 patients: 316 active, 320 morphine PCA	24 hours	S,E
C-2000-005	121 patients: all active	72 hours	S
C-2000-006	95 patients: all active	72 hours	S
C-2000-009	358 patients: all active	48 hours	S
C-93-023	253 patients: all active	48 hours	S
C-94-043	115 patients: all active	48 hours	S
C-95-019	78 patients: all active	48 hours	S
C-96-020	102 patients: all active	48 hours	S
FEN-INT-006	150 patients: all active	24 hours	S,P
C-92-038	14 patients: all active	24 hours	S,P
C-93-019	34 patients: all active	24 hours	S,P
C-94-060	70 patients: all active	24 hours	S,P
C-94-067	35 patients: all active	24 hours	S,P
C-94-068	28 patients: all active	72 hours	S,P
C-96-009	36 patients: all active	24 hours	S,P
C-97-001	40 patients: all active	24 hours	S,P
C-98-013	30 patients: all active	24 hours	S,P
C-2001-009	31 patients: all active	24 hours	S,P
C-2002-027	28 patients: all active	24 hours	S,P
C-2001-006	25 patients: all active	24 hours	P
C-95-034	24 patients	24 hours	S,W
C-95-050	24 patients	24 hours	S,W
C-95-051	24 patients	72 hours	S,W
C-95-053	24 patients	24 hours	S,W
C-96-003	111 patients	24 hours	S,W
C-94-057	83 patients	72 hours	S
C-94-058	85 patients	72 hours	S
C-94-059	21 patients	24 hours	S
C-96-055	27 patients	50 hours	S
C-96-056	8 patients	72 hours	S
C-96-057	3 patients	72 hours	S

[a]Code: S-safety, E-efficacy, P-pharmacokinetics, W-wear

C. Postmarketing Experience

While E-TRANS has not been marketed in any country thus far, the drug product fentanyl is widely marketed in oral/transbuccal, transdermal, and intravenous forms.

D. Literature Review

This reviewer examined a random sample of the provided references and concluded that ALZA has provided adequate support from the published literature for the use of patient controlled analgesia in patients experiencing moderate to severe pain.

V. Clinical Review Methods

A. How the Review was Conducted

Electronic files along with case report tables (CRTs) and case report forms (CRFs) were reviewed in whole or in part.

The study protocols, study reports and study results were reviewed for all supporting studies. The ISS was reviewed in depth. The data in the tables was compared with the data in the appendices. Each death was tracked backwards from the ISS through the appendices, narratives, CRTs and CRFs.

Data points from a random sample of adverse events were followed through the appendices, CRTs and CRFs.

ALZA's information on financial disclosure was reviewed.

B. Overview of Materials Consulted in Review

The division files for IND 41,574 were reviewed. The electronic New Drug Application (eNDA) submissions dated September 23 2003, November 14 2003, March 25 2004, and April 2 2004, April 16 2004, April 30 2004, May 13 2004, June 4 2004, June 11 2004, and July 1 2004 were also reviewed.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

No DSI audit was done as part of the clinical review. The data from most of the key tables in the study reports were cross-referenced with the study report listings and data from patient case report forms.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The trials were conducted in accordance with accepted ethical standards.

E. Evaluation of Financial Disclosure

ALZA has provided financial information from the investigators who participated in pivotal studies C-95-016, C-2000-007, C-2000-008 and C-2001-011.

Study C-95-016

This study was conducted before implementation of the regulations outlined in 21 CFR Part 54. In December 2001 ALZA obtained financial interest information from the principal investigators but was unable to obtain information from the sub-investigators despite due diligence.

ALZA has submitted financial disclosure form 3455 for
This form was submitted to disclose a ownership of greater than $50,000 worth of Johnson and Johnson stock. This form states that he is a
which enrolled 2%) of the randomized patients in this multi-center blinded trial.

ALZA has submitted financial disclosure forms 3455 for
and
This form was submitted to disclose a payment, on July 6th 2001, of $100,000 by Janssen Pharmaceutical Products to the
in the form of an unrestricted research grant. The
This site enrolled 1%) of the randomized patients in this multi-center blinded trial.

ALZA submitted certification with a form 3454 for the rest of the Principal Investigators and their sub-investigators. Although the clinical investigators had "not entered into any identifiable, disclosable financial arrangements with Johnson & Johnson or any of its affiliates" according to the provided form 3454, many of the investigators were missing financial disclosure forms at study initiation, at study closure and/or at one year post study follow-up.

C-2000-008

ALZA submitted certification with a form 3454 for the C-2000-008 Principal Investigators and their sub-investigators. Although the clinical investigators had not entered into any identifiable, disclosable financial arrangements with ALZA corporation according to the provided form 3454, many of the investigators were missing financial disclosure forms at study initiation, at study closure and/or at one year post study follow-up.

ALZA has submitted financial disclosure form 3455 for
This form was submitted to disclose a ownership of greater than $50,000 worth of Johnson and Johnson stock. This form states that he is a
which enrolled (5%) of the randomized patients in this multi-center blinded trial.

ALZA submitted certification with a form 3454 for the rest of the Principal Investigators and their sub-investigators. Although the clinical investigators had not entered into any identifiable, disclosable financial arrangements with ALZA corporation according to the provided form 3454, many of the investigators were missing financial disclosure forms at study initiation, at study closure and/or at one year post study follow-up.

Summary
The full financial disclosure information is missing from six Principal Investigators. The financial disclosure status of multiple sub-investigators is incomplete. The Sponsor confirms that no payments were made to investigators who did not return financial disclosure forms. The sponsor reports having performed due diligence to obtain the missing forms.

In light of the financial disclosure information provided by he data from his site was reviewed in detail. His stock ownership is unlikely to have influenced study outcome. The data provided from his site was consistent with the results from other sites. Drs. work at an institution which indirectly received an unrestricted research grant from Janssen over 60 days after the last patient was enrolled in the study. This payment, which was not made directly to either investigator, is unlikely to have influenced the study outcome.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

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.

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. 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.

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.

B. General Approach to Review of the Efficacy of the Drug

ALZA performed four pivotal trials in support of efficacy, see table 3. The protocols for these trials will be discussed in detail below. 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.

Table 3:
Trials submitted in support of efficacy of E-TRANS 40 mcg system

Trial	Study Design	Participants
C-95-016	single-center, randomized, double-blind, placebo-controlled, parallel-group	77 received fentanyl, 25 received placebo
C-2000-008	multi-center, randomized, double-blind, placebo-controlled, parallel-group	154 received fentanyl, 51 received placebo
C-2001-011	multi-center, randomized, double-blind, placebo-controlled, parallel-group	244 received fentanyl, 240 received placebo
C-2000-007	multi-center, randomized, open-label, active-controlled, parallel-group	316 received fentanyl, 320 received placebo

C-95-016 was a single-center, randomized, double-blind, placebo-controlled, parallel-group trial to evaluate the safety and efficacy of E-TRANS fentanyl (40 mcg on demand) for the management of postoperative pain in the first 24 hours after surgery.

C-2000-008 was a multi-center, randomized, double-blind, placebo-controlled, parallel-group trial to evaluate the safety and efficacy of E-TRANS fentanyl (40 mcg on demand) versus E-TRANS fentanyl (placebo) for the management of postoperative pain in the first 24 hours after surgery.

C-2001-011 was a multi-center, randomized, double-blind, placebo-controlled, parallel-group trial to evaluate the safety and efficacy of E-TRANS fentanyl (40 mcg on demand) for the management of postoperative pain in the first 24 hours after surgery.

C-20070-007 was a multi-center, randomized, open-label, active-controlled, parallel-group trial to compare the safety and efficacy of E-TRANS fentanyl (40 mcg on demand) to IV PCA morphine.

ALZA submitted seven uncontrolled studies in support of safety: C93-023; C-94-043; C-96-020; C-2000-005; C-2000-006; C-2000-009. Although efficacy descriptors were measured during these studies, open-label studies cannot be used to support efficacy so the results from those studies will not be discussed further in this section. The protocols from those studies are described in detail in Appendix B. The patient safety data from these studies will be discussed in Section VII, Integrated Review of Safety.

ALZA stopped six studies prematurely due to technical problems with the E-TRANS system: C-94-057; C-94-058; C-94-059; C-96-055; C-96-056; C-96-057. These studies were not analyzed for efficacy and will not be discussed further in this section. Detailed descriptions of these protocols may be found in Appendix B. The patient safety data from these studies will be discussed in Section VII, Integrated Review of Safety.

C. Detailed Review of Trials by Indication

C-95-016

Title:

The safety and efficacy of E-TRANS fentanyl (40 mcg on-demand) for the management of postoperative pain: A double-blind, single-center, placebo-controlled trial.

Objective:

- Compare the safety and efficacy of the E-TRANS fentanyl system with the E-TRANS placebo system in the management of the first 24 hours of post-operative pain

Population:

One hundred-two adult patients were randomized to treatment with 77 receiving active drug and 25 receiving placebo.

Inclusion criteria:

- Adults of either gender
- Post operative ASA I, II, III status, as defined in Appendix A
- Admission to the post-anesthesia care unit after surgery
- Expectation of moderate to severe pain requiring opioids for at least 24 hours post-operatively
- Awake patients breathing 8-24 breaths/minute spontaneously with an oxygen saturation of 90% or greater
- Patients who had been in the PACU for at least 30 minutes and had been titrated to comfort with intravenous opioids

Exclusion criteria:

- Patients expected to have post-operative analgesia supplied by a continuous regional technique
- History of allergy or hypersensitivity to fentanyl , skin adhesives and/or cetylpyridinium chloride
- Patients expected to need intensive care
- Patients expected to require additional surgery with 36 hours
- Known or suspected opioid tolerance
- History of opioid dependence within 3 months of starting the study
- Active systemic skin disease
- Increased intracranial pressure
- Illicit drug use, prescription drug abuse or alcohol abuse within 14 days before the start of the study
- Pregnancy

Study design:

A single-center, double-blind, placebo-controlled, parallel-group trial conducted in New Zealand.

Study duration:
24 hours per participant

Study procedure:
Once patients recovered from anesthesia (general or regional), they were to be titrated to comfort using intravenous morphine, fentanyl, sufentanil or alfentanil.

Patients who were eligible for study participation were to be randomized to receive either E-TRANS fentanyl or E-TRANS placebo for the next 24 hours. The application site was to be wiped with an alcohol swab and then allowed to dry prior to application of the E-TRANS system. 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. If less than 75% of the surface area of the E-TRANS system was adhered to the skin, hypoallergenic tape was to be used to secure the E-TRANS system in place. Intravenous fentanyl was allowed as rescue medication during the first three hours after study system application.

During the study period, the following assessments were to be made: number of on-demand doses, vital signs, oxygen saturation, E-TRANS system adherence, and pain intensity measurements done prior to titration with intravenous opioids, before application of the study system , at 0.5-, 1-, 2-, 3- , 4-, 6-, 8-, 12-, 16-, 20- and 24 hours. At the termination of the study period, patient and investigator were to give their global assessments of the therapy.

Patients were to be considered study completers if one of the following conditions occurred:

- The E-TRANS system was worn for the study period of 24 hours
- 80 on-demand doses had been delivered (the maximum number of doses/system)
- Pain control was considered inadequate
    - The staff monitored the delivery of an on-demand dose to ascertain successful operation of the E-TRANS system by the patient and proper E-TRANS system functioning
    - Ten minutes after watching the patient successfully deliver an on-demand dose, the staff were to ask whether the patient has a reduction in pain. If the pain was not reduced and fewer than 3 hours had elapsed since treatment initiation, the patient could be retitrated to comfort using intravenous doses of fentanyl.
    - If more than 3 hours had elapsed since treatment initiation, the patient would be withdrawn from the study.
- The E-TRANS system was suspected of having a technical failure

The first subject was treated on this protocol on January 22 1997 and the last treatment was completed on September 16 1997. The first three amendments to the protocol were made prior to enrolling any patients in this study. The subsequent amendments were made after the study had started.

- Amendment 4, dated February 26 1997, updated the E-TRANS fentanyl operating instructions and removed the requirement to report all adverse events that occurred within 30 days of study drug dosing to ALZA. Serious adverse events that occurred within that time were still to be reported.
- Amendment 5, dated April 30 1997, detailed the instructions for return of the used and unused E-TRANS systems, clarified that rescue medication use should be entered on the Rescue Medication CRF not the concomitant medications CRF, clarified that a secondary analysis of the primary efficacy parameter including all randomized patients with data would be performed, clarified the logistic regression analysis and updated the E-TRANS fentanyl operating instructions. (*Reviewer's note: The company was asked if they examined the CRFs completed prior to this amendment to make certain that rescue medication use had been properly entered. The Agency was awaiting their response as of 5/03/04.*)
- Amendment 6, dated August 26 1997, excluded patients with known hypersensitivity to nickel or metal jewelry since nickel and copper salts were noted to appear within the cathode hydrogels of some systems.

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

- Pain intensity
- Patient/Investigator global assessments
- Number of on-demand doses delivered
- Number of patients requiring re-titration to comfort
- Assessment of the adherence of the E-TRANS system

Study results:

Description of patients:

Of the 144 patients who were screened, 102 were eligible for trial entry and randomization: 77 (76%) received E-TRANS fentanyl and 25(25%) received E-TRANS placebo.

Demographics

The evaluable population, defined as those who completed at least three hours on the study, included 99 patients, 77 of whom received E-TRANS fentanyl. Three patients who had been using E-TRANS placebo were not evaluated due to suspected system technical difficulties. The evaluable patients were predominantly Caucasian (n=78) with the rest described as Hispanic (n=1) or other (n=20). The majority were female (n=82). The majority of the patients (n=73) had lower abdominal surgery (bowel, genitourinary or gynecological). Twenty-three had orthopedic surgery. Three had upper abdominal surgery. There were no statistically significant demographic differences found when the patients who received E-TRANS fentanyl were compared to those who received E-TRANS placebo.

Table 4:
Demographics summary table of the 99 evaluable patients[a]

	Fentanyl (n=77)	**Placebo (n=22)**	**Total(n=99)**
Gender			
Female	63 (82%)	19 (86%)	82 (83%)
Male	14 (18%)	3 (14%)	17 (17%)
Age			
Median	46	43	45
Range	23-75	21-68	21-75
Surgery			
Lower abdominal	58 (75%)	15 (68%)	73 (74%)
Upper abdominal	3	0	3
Orthopedic	16 (21%)	7 (32%)	23 (23%)
ASA status			
I	56 (73%)	18 (82%)	74 (75%)
II	19 (25%)	4 (18%)	23 (23%)
III	2 (3%)	0	2 (2%)

[a]The numbers for this table are taken from Tables F and G in the amended final report for this study.

Patient disposition

Nine (12%) of the patients in the E-TRANS fentanyl group discontinued prior to 24 hours of system use: six due to inadequate pain control after the first three hours; two due to adverse events (1081-nausea at study hour 11, 1101-nausea at study hour 5); one due to erroneous early removal of the system at 23 hours. One patient (1075), who used 80 doses prior to the end of the 24 hour study period, was considered to have completed the study. Twelve (48%) of the patients in the placebo group discontinued prematurely: nine due to inadequate pain control after the first three hours; three due to suspected technical failure.

Table 5:
Patient disposition for study C-95-016

Disposition	Total	E-TRANS fentanyl	Placebo
Patients screened	144		
Patients enrolled	102	77	25
Patients who discontinued	21	9 (12%)	12 (48%)
Inadequate pain control	15		
Discontinuation at ≤3 hours		0	0
Discontinuation at >3 hours		6 (8%)	9 (41%)
Adverse events	2	2 (3%)	0
Erroneous early system removal	1	1 (1%)	0
Suspected system failure	3	0	3 (12%)
Patients who completed the study	81	68 (88%)	13 (52%)

Protocol violations:
Six patients were enrolled who did not meet the entry criteria. One patient in the E-TRANS had an elastoplast allergy (1003). Five patients, all of whom were scheduled for hysterectomy, did not have screening pregnancy tests performed: four in the E-TRANS fentanyl group (1002, 1005, 1009, 1010) and one in the E-TRANS placebo group (1001). An additional protocol violation occurred during the study. One patient (1001) received three doses of intravenous fentanyl as rescue medication between 5 and 5.25 hours after application of E-TRANS. This patient was withdrawn from the study after 6 hours due to inadequate pain control during the first 3 hours of study.

Reviewer's note:
The omission of pregnancy tests in patients scheduled for hysterectomy would have no bearing on analgesic efficacy. Elastoplast allergy might make the patient more susceptible to an application site reaction but this is a possibility that would weigh against the E-TRANS system, not in its favor. The administration of additional rescue medication to a patient using the E-TRANS placebo system would also weigh against the E-TRANS system not in its favor. The described protocol violations do not affect the interpretation of the presented efficacy data.

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

Pharmacokinetics
Blood sampling was done to confirm delivery of fentanyl. One sample was collected between 4 and 7 hours after treatment initiation, just prior to an on-demand dose and another sample was drawn 15 minutes later. Serum fentanyl doses were determined to increase after on-demand dosing, which is consistent with drug having been delivered. The ratio of serum fentanyl concentration postdose/predose was higher in the active group (1.07) than in the placebo group (0.89).

Efficacy results:
In the study report, ALZA discusses the 99 patients evaluated for efficacy. The first three hours (Hours 0-3) after application of the E-TRANS system were not used to evaluate E-TRANS efficacy alone since rescue medication was allowed during that time.

Three patients, all in the E-TRANS placebo group, were discontinued from the study in under 3 hours due to E-TRANS system malfunctions and were not part of the predefined evaluable patients used for the efficacy analysis.

Reviewer's note:
Inclusion of results from the 3 placebo patients who were discontinued early may have biased the results toward the active drug since the dropouts from the placebo group would have increased from 9 to 12, a percentage increase from 41% (9/22) to 54% (12/22). The exclusion was appropriate.

Primary efficacy measurement

Discontinuations due to inadequate pain control

The sponsor defined this measure as the number of patients in each treatment group who dropped out of the study more than three hours after application of study therapy due to inadequate pain control. The use of an evaluable population, i.e. those who remained in the study for more than 3 hours, for the primary efficacy analyses instead of an intent-to-treat population was specified in the original protocol.

Fifteen patients withdrew from the study because of inadequate pain control after the first three hours on study: 6 of the 77 patients in the E-TRANS fentanyl group (8%) and 9 of the 22 patients in the E-TRANS placebo group (41%). The difference in dropout rate was statistically significant with a p-value of 0.0001.

Table 6:
Patients who discontinued due to inadequate pain control[a]

Patient #	Surgery	Hours on study	Flashes	Delivered doses, %available doses
Fentanyl group				
1005	Lower abdominal surgery	18.2	5	25, 31%
1035	Lower abdominal surgery	14	2	10, 13%
1042	Orthopedic surgery	3.7	3	15, 63%
1093	Lower abdominal surgery	12.2	5	25, 42%
1099	Lower abdominal surgery	3.7	3	15, 63%
1102	Orthopedic surgery	4.8	4	20, 67%
Placebo group				
1001	Lower abdominal surgery	6	5	25, 69%
1008	Orthopedic surgery	4.3	3	15, 63%
1033	Lower abdominal surgery	7.2	5	25, 83%
1038	Lower abdominal surgery	5.3	3	15, 50%
1051	Lower abdominal surgery	14.6	6	30, 38%
1055	Lower abdominal surgery	3.6	3	15, 60%
1061	Lower abdominal surgery	6.9	5	25, 60%
1096	Orthopedic surgery	6.3	5	25, 69%
1100	Lower abdominal surgery	15.4	7	35, 44%

[a]This table was derived from information presented in Table 12.2.1.2 in the study report. This reviewer converted the number of flashes at a ratio of five doses/flash to determine the doses delivered. The number of available doses was calculated as 6 times the number of study hours (rounded to the nearest whole number). However, the maximum denominator used was 80 since the system only allowed 80 doses to be delivered.

The use of rescue medication during the first three hours of E-TRANS use was associated with study discontinuation because of inadequate pain relief. Using logistic regression as pre-specified in the protocol, ALZA demonstrated an odds ratio of 2.989 (CI 0.808, 11.06) for discontinuation for patients using rescue medication in the first three hours.

ALZA performed a logistic regression of dropouts for any reason, an efficacy analysis which was not specified in the initial protocol. In this analysis the 9 active group patients who dropped out were compared to the 9 placebo group patients who dropped out. The table below describes the subset of patients who dropped out for any reason and received rescue medication in the first three hours of the study. Patients who received rescue medication within the first three hours were found to be more likely to discontinue the study (OR 3.25 CI 1.061, 9.952).

Table 7:
Patients who dropped out for any reason and the amount of rescue used[a]

Patient #	Surgery	Fentanyl rescue dose	# rescue doses
Fentanyl group			
1007[b]	Lower abdominal surgery	20 mcg	2
1042[c]	Orthopedic surgery	20 mcg	8
1099[c]	Lower abdominal surgery	20 mcg	2
1101[d]	Lower abdominal surgery	20 mcg	3
1102[c]	Orthopedic surgery	20 mcg	9
Placebo group			
1001[e]	Lower abdominal surgery	20 mcg	3
1033	Lower abdominal surgery	20 mcg 10 mcg	3 1
1055	Lower abdominal surgery	20 mcg	9
1061	Lower abdominal surgery	20 mcg	5
1100	Lower abdominal surgery	20 mcg	3

[a]This table was derived from information presented in Table 12.2.4.2 in the study report.
[b]This patient was discontinued because her patch was removed prematurely after 23 hours.
[c]This patient was discontinued due to inadequate pain relief
[d]This patient was discontinued due to an adverse event, nausea/vomiting.
[e]Patient 1001 represented a protocol violation as she received rescue medication up until hour 5 of the study.

Secondary efficacy measurements

Pain intensity

The pain intensity was measured using a 100-mm visual analog scale (VAS) with the ends representing no pain (0) and worst possible pain (100). Measurements were made immediately prior to titration with intravenous analgesia, immediately before the application of the E-TRANS system, and at 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 20, 24 hours after application.

After the study was unblinded, it was noted that approximately 6% of the pain assessments were missing. ALZA did not analyze the mean pain intensity over the 24-hour treatment period, opting instead to compare the last pain intensity score. ALZA reports that dropouts were not replaced nor were adjustments made for missing data.

The mean VAS scores in the active group decreased from baseline(hour 0) to the last observation as opposed to the placebo group in which the mean scores were effectively unchanged (active: 31.6 to 20.6, placebo 36.5 to 37.3). Using ANOVA, the sponsor found a p-value of 0.0006 for this difference.

Table 8:
Pain intensity scoring over time[a]

Study hour	E-Trans fentanyl (n=77)			Placebo (n=22)		
	#patients	#patients with VAS scores	Mean VAS (SEM)	#patients	#patients with VAS scores	Mean VAS (SEM)
0	77	77	31.6 (1.51)	22	22	36.5 (2.85)
1	77	77	32.8 (2.01)	22	22	43.3 (4.24)
2	77	77	34.3 (1.84)	22	22	44.1 (4.11)
3	77	77	31.6 (1.88)	22	21	40.2 (4.12)
4	77	**74**	**31.8 (1.99)**	**22**	**20**	**36.1 (4.28)**
6	74	65	28.4 (2.48)	20	17	32.8 (5.04)
8	74	63	22.3 (2.02)	16	13	28.8 (4.42)
12	74	58	21.1 (2.16)	15	13	28.2 (5.55)
16	72	61	21.8 (2.03)	15	13	22.8 (6.22)
20	70	69	19.8 (2.07)	13	13	23.5 (4.70)
24	**68**	**67**	**18.2 (1.84)**	**13**	**13**	**25.5 (6.17)**
Last observation VAS		77	20.6 (1.93)		22	37.3 (5.76)

[a]This table is a modification of table 11.2.3.6 in the study report.

Reviewer's note:
Since rescue use was allowed through Hour 3, I do not consider the first three study hours to represent a test of E-TRANS analgesia alone. However, when the available Hour 4 VAS scores are considered (presented in bold in the table above) and compared to the available mean VAS scores at hour 24(presented in bold in the table above), the difference in mean VAS scores between the active and placebo groups is still apparent (active: 31.8 to 18.2, placebo 36.1 to 25.5). While this comparison does not account for early discontinuations, it incorporates data from all of the placebo group patients who completed 24 hours of study and 67 of the active group patients. One patient in the latter group had her E-TRANS system removed at 23 hours instead of 24 hours as called for in the protocol.

What remains unexplained is the early difference between the VAS scores in the two groups. At baseline and during the first three hours, when rescue was available to both groups, the VAS scores are higher in the placebo group with a wider range of values. Since the demographics for the groups were similar, differences in age, gender, or type of surgery cannot be the explanation for the consistently higher scores during the first three hours. The differences seen did reach statistical significance so ALZA was asked to

provide additional data for analysis so that we could adjust for the difference to determine whether the difference in the last observation VAS scores remained significant. Our analysis of the additional data provided showed that the difference remained significant.

Number of on-demand doses delivered

The number of on-demand doses delivered was recorded after the pain intensity assessments. The estimated number of doses administered was calculated as 5 times the number of LED flashes minus 2. ALZA notes that this provides a margin of error of +/- 2.

When the entire study period was reviewed, the number of doses per patient per hour was almost identical in the active and placebo groups, 1.7 and 1.8 respectively. The mean total number of doses over the study period was slightly higher in the active group when compared to the placebo group, 38 and 31 respectively.

Demand for fentanyl doses was highest in both groups during the first 6 hours postoperatively.

Table 9:
Number of on-demand doses/patient by hours post-enrollment[a]

	E-TRANS(fentanyl) 40 µg (n=77)				Placebo (n=22)			
Hours Post-enrollment	No. of patients	No. of LED flashes/ patient	No. of estimated doses/ patient	No. of estimated doses/patient/ hour	No. of patients	No. of LED flashes/ patient	No. of estimated doses/ patient	No. of estimated doses/patient/ hour
1	77	0.97	3.03	3.03	22	0.95	2.95	2.95
2	77	1.52	5.62	2.81	22	1.55	5.82	2.91
3	77	1.95	7.77	2.59	22	2.09	8.55	2.85
4	75	2.32	9.63	2.41	21	2.43	10.24	2.56
6	74	3.00	13.00	2.17	19	3.11	13.63	2.27
8	74	3.62	16.11	2.01	16	3.47	15.33	1.92
12	73	4.79	21.97	1.83	15	4.40	20.00	1.67
16	70	6.11	28.57	1.79	13	5.31	24.54	1.53
20	69	7.42	35.10	1.76	13	6.69	31.46	1.57
24	67	8.34	39.72	1.65	13	7.85	37.23	1.55
Last dose	77	8.03	38.13	1.69	22	6.55	30.73	1.77

Note: Estimated number of on-demand doses = 5 times number of LED flashes minus 2. If LED flashes = 0 then estimated number of on-demand doses = 0.

[a]This table is taken from the study report, Table 11.2.4.2

Number of patients requiring re-titration to comfort

Patients who experienced inadequate pain control during the first three hours after initiating use of the study system were allowed to receive intravenous rescue doses of fentanyl.

The use of rescue medication was similar in the active and placebo groups. In the active group, 34% (n=26) of the participants required rescue medication. The mean cumulative rescue fentanyl dose in this group was 78.5 mcg (range 20-220 mcg). In the placebo

group, 36% (n=8) of the participants required rescue medication. The mean cumulative rescue fentanyl dose in this group was 76.3 mcg (range 20 to 180 mcg).

Patient global assessment

This categorical evaluation was determined at the time of study termination. Patients were asked to respond to the following question: " Overall would you rate this method of pain control since the time the E-TRANS system was applied as being poor, fair, good, or excellent."

The patients who responded excellent or good were considered successes while those who responded fair or good were considered failures. Over 75% of people receiving active drug and almost 60% of people receiving placebo considered their treatment successful. Using chi-square testing, the between-treatment comparison was found to be statistically significant with a p-value of 0.0008 for the combined response and a p-value 0.0006 for each category of response.

Table10:
Patient global assessments of therapy[a]

	Success	Failure
E-TRANS fentanyl	90%	10%
E-TRANS placebo	59%	41%

[a]The numbers in this table were derived from Table 11.2.3-8, p.102 of the study report

Investigator global assessment

This categorical evaluation was determined at the time of study termination. Investigators were asked to respond to the following question: " Overall would you rate this method of pain control for this patient since the time the E-TRANS system was applied as being poor, fair, good, or excellent."

Table11:
Investigator global assessments of therapy[a]

	Success	Failure
E-TRANS fentanyl	90%	10%
E-TRANS placebo	59%	41%

[a]The numbers in this table were derived from Table 11.2.3-9, p.103 of the study report

Since the results for this efficacy parameter are identical to the results from the patient global assessment, it is presumed that the statistical analysis would produce the same result. Using chi-square testing, we would expect to find that the between-treatment comparison was statistically significant for the combined response and for each category of response.

Reviewer's note:
Although the percentage of the patients in each group rated as a success or as a failure was identical in the patient assessments and the investigator assessments, when the

individual records were reviewed, six discordant assessments were recorded per treatment arm. Three cases in each treatment arm had a patient reported failure matched to an investigator reported success. The other three cases in each arm had a patient reported success matched to an investigator reported failure. The discordant assessments were not biased against or in favor of the drug product.

Assessment of the adherence of the E-TRANS system

The system adhesion was assessed just prior to removal. If the system had been taped due to having 25% or less of the surface area adherent, N/A was recorded. Otherwise the following scale was used:

- 0=system adhered to at least 90% of the area and no edges were unattached
- 1=System between 75 and 89% adhered
- 2=System between 50 and 74% adhered
- 3=System less than or equal to 49% adhered or no longer adhered to the skin

In most cases at least 90% of the system was adherent with no unattached edges, see table below. Even though 24% had below 90% of the patch adherent, these patients were not seen to have had a decrease in efficacy or an increase in adverse events.

Table 12:
System adherence

System Adherence[a]
(Evaluable Patients)

	Treatment Group		
	E-TRANS (fentanyl) 40 µg (n=77)	Placebo (n=22)	Total (n=99)
Number of Systems Used	77 (100%)	22 (100%)	99 (100%)
System adhered to at least 90% of the area and no edges unattached	60 (77.9%)	18 (81.8%)	78 (78.8%)
System between 75% and 89% adhered	11 (14.3%)	1 (4.5%)	12 (12.1%)
System between 50% and 74% adhered	2 (2.6%)	0	2 (2.0%)
System less than or equal to 49% adhered of system no longer adhered to skin	1 (1.3%)	0	1 (1.0%)
System taped	3 (3.9%)	3 (13.6%)	6 (6.1%)

[a] System adherence status was checked just prior to removal.

Reviewer's conclusions from the efficacy results in study C-95-016

This study has 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. It has not demonstrated clear efficacy during the first three postoperative hours since in both the active and the placebo groups approximately one-third of the patients required rescue medication (34% and 36%

respectively). The fact that 1/3 of the patients who were receiving active drug via E-TRANS required supplemental parenteral fentanyl implies that the E-TRANS unit was not adequately providing analgesia in those patients over that time period.

The predefined primary efficacy measurement was the number of discontinuations due to inadequate pain control after the first three hours of the postoperative period. In the group receiving E-TRANS fentanyl 8% dropped out while in the group receiving E-TRANS placebo 41 % dropped out. This difference, which was calculated using the respective evaluable populations as the denominators, is clinically and statistically significant.

If one examines the patients who discontinued in each group to determine what percentage of the group left the study due to inadequate analgesia, i.e. use the number of patients who discontinued as the denominator and the number who discontinued for inadequate analgesia as the numerator, a difference is still apparent. In the E-TRANS group, 6/9 discontinued for inadequate analgesia after 3 hours on study, 67%. In the placebo group, 9/12 discontinued for inadequate analgesia after 3 hours on study, 75%. This is consistent with the conclusion that the E-TRANS fentanyl system was providing some benefit over placebo.

The predefined secondary efficacy measurements trended towards agreement with the primary efficacy measurement. Pain intensity over time was significantly lower in the active treatment arm. The investigator and patient global assessments were consistent with successful treatment by the active drug.

C-2000-008

Title:

The safety and efficacy of electrotransport (E-TRANS) fentanyl for the management of postoperative pain: A double-blind, multi-center, placebo-controlled trial.

Objective:

- Compare the safety and efficacy of the E-TRANS fentanyl system with the E-TRANS placebo system in the management of the first 24 hours of post-operative pain

Population:

Two hundred-five adult patients were randomized to treatment (3:1::active:placebo) with 154 receiving active drug and 51 receiving placebo.

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 (PACU) after 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 breathing 8-24 breaths/minute spontaneously with an oxygen saturation of 90% or greater

Exclusion criteria:

- Patients expected to have post-operative analgesia supplied by a continuous regional technique
- 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 14 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

Study design:
A multi-center, double-blind, placebo-controlled, parallel-group trial conducted in the Unites States of America.

Study duration:
24 hours per participant

Study procedure:
After 30 minutes in the PACU, vital signs and oxygen saturation were to be assessed along with pain intensity. The pain intensity score obtained at that assessment was designated the PACU score. Patients who were eligible for study participation, i.e. those who had been in the PACU for at least 30 minutes and were awake alert and comfortable, were to be randomized to receive either E-TRANS fentanyl or E-TRANS placebo for the next 24 hours. Pain intensity, vital signs and oxygen saturation were to be assessed just prior to application of the study system (Hour 0). The baseline score was defined as the pain intensity score at Hour 0.

The assigned treatment system was to be applied immediately after the Hour 0 assessment. The application site was to be wiped with an alcohol swab and then allowed to dry prior to application of the E-TRANS system. 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 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, as well as number of on-demand doses, vital signs, oxygen saturation, and E-TRANS system adherence. If a patient did not complete the full 24-hour study period, pain intensity measurements and global assessments were to be completed at the time of withdrawal. Otherwise, patients and investigators were to give their global assessments of the therapy at the time of treatment termination.

Patients were considered to have completed the study if one of the following conditions occurred:

- The E-TRANS system was worn for the study period of 24 hours
- 80 on-demand doses had been delivered (the maximum number of doses/system)

Patients were to be withdrawn from the study for any of the following:

- Pain control was considered inadequate
- Two E-TRANS systems in a given patient were suspected of having technical failures (original and a replacement)
- Patient withdrew consent

- Major protocol violation or significant protocol deviation
- Patient had an immediate life-threatening event
- Patient had 2 episodes of clinically relevant respiratory distress

Patients who withdrew during the first 3 hours of the study were to be replaced until at least 123 evaluable patients had accrued in the E-TRANS treatment group and at least 41 evaluable patients in the placebo group. The protocol defined the evaluable population as those who received at least 3 hours of treatment with a study system.

The first subject was treated on this protocol on September 18 2000 and the last treatment was completed on January 30 2001. The first amendment to the protocol was made prior to enrolling any patients in this study. The second amendment was made after the study had started.

- Amendment 2, dated December 15 2000, increased the number of patients to be enrolled and the percent dropout rate from 184 and 10% to 216 and 30%. The sponsor stated that a higher than expected early discontinuation rate (prior to Hour 3) was being seen so the sample size had to be increased.

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
  Only data from evaluable patients, i.e. those who had at least three hours of treatment with a study system, would be used for this analysis.

Secondary efficacy measurements

- Overall dropout rate regardless of termination reason during the 24-hour study period
- Mean pain intensity over the 24-hour treatment period (0-100 VAS)
  If a patient withdrew prior to a scheduled pain intensity assessment, the measurement at the time of withdrawal would be carried forward to the scheduled pain intensity assessment. 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 VAS was considered missing when the patient was asleep. In the case of premature discontinuation, the mean pain intensity was to be computed only up to the time of removal.
- Investigator global assessment (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.
- Patient global assessment (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.

Study results:

Description of patients:

Of the 232 patients who were screened, 205 were eligible for trial entry and randomization: 154 received E-TRANS fentanyl and 51 received E-TRANS placebo. Sixteen patients were withdrawn from the study due to inadequate analgesia in the first three hours, 8% of the E-TRANS fentanyl (12/154) group, and 8% of the placebo (4/51) group. The evaluable population, i.e. those who completed at least 3 hours of treatment with the study system, included 189 patients, 142 of whom received E-TRANS fentanyl.

The evaluable patients were predominantly Caucasian (n=154/189, 82%) with the rest described as black (n=22), Hispanic (n=11), Asian (1) or other (1). The majority of the evaluable patients were female (n=130, 69%). The majority of the patients treated (n=107/205, 52%) had lower abdominal surgery (bowel, genitourinary or gynecological). Seventy-four had orthopedic surgery. Eighteen had upper abdominal surgery. Two had thoracic/chest surgery. The remaining four had other surgeries. There were no significant demographic differences between the group which received fentanyl and the group which received placebo.

Table 13:

Demographics summary table of the 189 evaluable patients[a]

	Fentanyl (n=142)	**Placebo (n=47)**	**Total(n=189)**
Gender			
Female	98 (69%)	32 (68%)	130 (69%)
Male	44 (31%)	15 (32%)	59 (31%)
Age			
Median	49	57	49
Range	20-88	20-79	20-88
Race			
Caucasian	113 (80%)	41 (87%)	154 (82%)
Black	17 (12%)	5 (11%)	11(12%)
Asian	1 (1%)	0	1 (1%)
Hispanic	10 (7%)	1 (2%)	11 (6%)
Other	1 (1%)	0	1 (1%)
Surgery			
Lower abdominal	75 (53%)	25 (49%)	107 (52%)
Upper abdominal	12 (8%)	6 (12%)	18 (9%)
Orthopedic	50 (35%)	19 (40%)	69 (37%)
Thoracic/Chest	2 (1%)	0	2 (1%)
Other	4 (3%)	0	4 (3%)
ASA status			
I	25 (18%)	6 (13%)	31 (16%)
II	77 (64%)	32 (71%)	109 (66%)
III	2 7(22%)	8 (18%)	35 (21%)

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

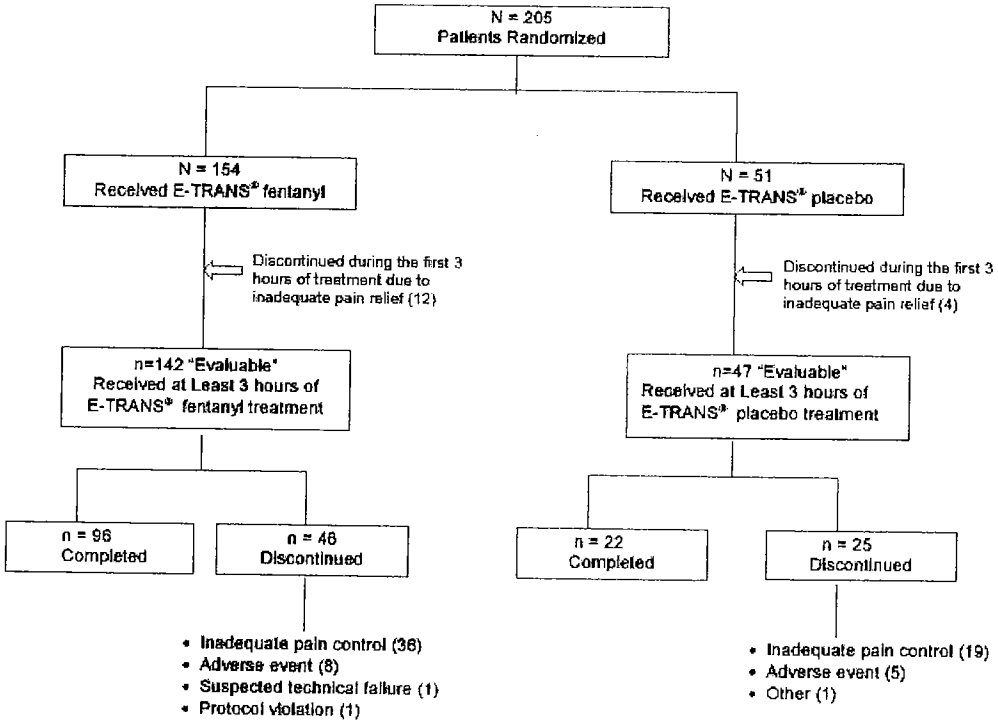
Patient disposition

Forty-six (32%) of the patients in the E-TRANS fentanyl group discontinued prior to 24 hours of system use: 36 (78%) due to inadequate pain control after the first three hours; 8 (17%) due to adverse events (411-nausea, 604-back pain ,614-nausea, 1212-nausea,1302-pruritis, nausea/vomiting, pain at operative site,1320-sedation/tremor,1402-headache, 1424-dyspnea); one (2%) due to a protocol violation (Vicodin was given during the study and the early termination VAS was not completed-pt 321); one (2%) due to a suspected technical failure-pt 1024.

Twenty-five (53%) of the patients in the placebo group discontinued prematurely: 19 (76%) due to inadequate pain control after the first three hours; 5 (20%) due to adverse events (602-dizziness,1115-back pain, 1208-bladder spasms, 1311-sciatica, 1324-back spasms) and 1 (4%) due to an "other reason" (534).

One patient (309) required more than 80 doses in the 24 hour period. A second E-TRANS fentanyl system was applied after 80 doses had been administered by the first system.

Table 14:
Patient disposition[a]



Source: Tables 11.2.2-1 and 11.3.2-1.

[a]This table was cross-referenced with table 12.2.1.2 from the study report.

Protocol violations:
Two patients were enrolled who did not meet the entry criteria. Two patients had received an investigational drug within 30 days of study onset or were enrolled in another investigational study (1107,1416).

An additional 41 protocol violations, most of which were missed or delayed study assessments, occurred during the study. However, there were 6 patients (4 on E-TRANS fentanyl, 2 on E-TRANS placebo) who received prohibited analgesics while on study: Vicodin (321); Percocet (607); Demerol (1020, 1416); Naproxen (1301); Toradol (327). Patient 522 (E-TRANS fentanyl) had a treatment related SAE but no blood sample for fentanyl concentration was drawn during her extended hospitalization for nausea. ALZA did not exclude any patients with known protocol violations from the efficacy and safety analyses.

Ten systems were suspected to have had technical failures. All ten patients had been on study more than three hours and were included in the analyses as evaluable patients. The reported technical problems were as follows:

- Continuous beeping (4 systems, patients 807, 809, 1024, 1313)
- No LED flash at dose initiation (4 systems, patients 506, 534, 1210,1416)
- No beep (1 system, patient 1315)
- No dose administered after 3 attempts (1 system, patient 1303)

Alza's analysis of the systems revealed

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

Pharmacokinetics
No blood sampling was done in this study.

Efficacy results:
In addition to the planned analyses discussed above under outcome measures, two post-hoc analyses were conducted by ALZA after unblinding of the data. The inclusion criteria specified that patients being enrolled in this study should be awake, alert and comfortable after 30 minutes in the PACU having received parenteral opioids if needed for comfort. A pain intensity score was to be determined at 30 minutes or more after PACU arrival. That score was designated the PACU score.

- Nineteen percent (39/205)of the patients enrolled in this study had a PACU score of 75 or more despite the protocol requirement that patients were supposed to be

comfortable prior to enrollment. A dichotomous variable for PACU pain was added to the planned logistic regression models, i.e. PACU pain greater than/equal to or less than 75.

- An additional logistic regression analysis using backward selection which did not force the effect of each variable to be estimated in the presence of treatment , allowing unrestricted elimination of variables.

Reviewer's note:
A patient reporting a score of ≥75 on a scale anchored by absence of pain at zero and worst possible pain at 100 should not have been considered comfortable. Since comfort in the PACU was one of the inclusion criteria, patients who were not comfortable should have been excluded from study participation. In hindsight, it would have been appropriate for ALZA to designate a maximum pain intensity PACU score for study inclusion. ALZA has attempted to address this by performing a posthoc analysis excluding patients who did not meet the inclusion criteria for initial levels of comfort.

Primary efficacy measurement

Discontinuations due to inadequate pain control

The sponsor defined this measure as the number of patients in each treatment group who dropped out of the study more than three hours after application of study therapy due to inadequate pain control. The use of an evaluable population for the primary efficacy analyses instead of an intent-to-treat population was specified in the original protocol.

Fifty-four patients withdrew from the study because of inadequate pain control after the first three hours on study: 36 of the 142 evaluable patients in the E-TRANS fentanyl group (25%) and 19 of the 47 evaluable patients in the E-TRANS placebo group (40%). The difference in dropout rate was statistically significant with a p-value of 0.0486. The mean duration of treatment prior to discontinuation was similar, 6.5 and 6.6 hours in active and placebo groups respectively.

In the planned secondary analysis of all treated patients (n=205), 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. In a posthoc analysis of all treated patients with a PACU score of less than 75, a statistically significant treatment group difference was found with a p-value of 0.014: 30/121 dropped out in the fentanyl group; 20/45 dropped out in the placebo group.

As specified in the protocol, an exploratory logistic regression analysis adjusting for potential baseline confounding factors e.g. treatment, age, gender, race and patient requirement for rescue medication within the first three hours after treatment initiation. while retaining variables with significant impact on the response variable, withdrawal due to inadequate pain control was performed. Evaluable patients on active treatment were less likely than persons in the placebo group to withdraw due to inadequate pain control, odds ratio (OR) of 0.471. All treated patients who received rescue medication in the first three hours were more likely to discontinue the study then those who did not use rescue

medication, OR 3.836. There was no statistically significant difference between treatment groups in the number of patients who required rescue medication during the first three hours of the study. The mean cumulative doses of rescue medication were similar between treatment groups.

As part of a posthoc analysis, ALZA introduced a variable for PACU pain score <75 or ≥75. Patients with PACU scores >75 were more likely to drop out, OR 2.222.

Table 15:
Withdrawals due to inadequate pain relief (study report p.68)

	E-TRANS fentanyl	E-TRANS placebo
All treated patients	154	51
Withdrawals	48 (31%)	23 (45%)
Evaluable patients	142	47
Withdrawals	36 (25%)	19 (40%)
Patients with PACU pain < 75	121	45
Withdrawals	30 (25%)	20 (44%)

Secondary efficacy measurements

Pain intensity

The protocol specified that 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. Measurements were made after the patient had been in the PACU for 30 minutes and was awake, alert and comfortable, immediately before the application of the E-TRANS system, and at 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 20, 24 hours after application. The VAS score was considered missing when the patient was asleep.

If a patient withdrew prior to a scheduled pain intensity assessment, a measurement was made at the time of withdrawal which would then be carried forward to the scheduled pain intensity assessment. In the case of premature discontinuation, the mean pain intensity was to be computed only up to the time of removal.

Approximately 20% of the pain assessments were missing (n= 368, 292/1382 in the E-TRANS fentanyl group, 76/402 in the E-TRANS placebo group) so ALZA did not analyze the mean pain intensity over the 24-hour treatment period, and opted instead to use the last pain intensity score to assess the difference in pain between the groups.

Using the last mean pain intensity VAS scores, ALZA determined that there was no statistical significant difference in the treatment groups when the data from all treated patients (intent-to-treat population) was reviewed. The mean VAS for the active group was 33.7 (SE 2.38) while the mean VAS for the placebo group was 43 (SE 4.41). p-value 0.0571.

A statistically significant difference was seen in the treatment groups when the data from all evaluable patients was reviewed. The mean VAS for the active group was 30.9 (SE 2.39) while the mean VAS for the placebo group was 40.8 (SE 4.61), p-value 0.0474.

A highly significant difference was seen in the post hoc analysis of the data from the 121 patients with a PACU score of less than 75. The mean VAS for the active group was 29 (SE 2.53) while the mean VAS for the placebo group was 42.5 (SE 4.76), p-value 0.0083.

ALZA used the mean change from baseline (hour 0) to a last observed VAS to do their calculations, however since rescue use was allowed through Hour 3, the first three hours on treatment do not represent a test of E-TRANS analgesia alone. When the available Hour 4 VAS scores are considered (presented in bold in the table below) and compared to the available mean VAS scores at hour 24, the difference in mean VAS scores between the active and placebo groups is small (active: 33.3 to 18.5, placebo 41.9 to 19.4). This comparison incorporates data from all of the evaluable placebo group patients who completed 24 hours of study and 88/96 of the evaluable active group patients who completed 24 hours of study. The result does not change appreciably when data from Hours 4 and 24 in the patients with PACU scores less than 75 are analyzed.

Table 16:
Pain intensity scoring over time in evaluable patients[a]

Study hour	E-Trans fentanyl (n=142)			Placebo (n=47)		
	#patients	#patients with VAS scores	Mean VAS (SEM)	#patients	#patients with VAS scores	Mean VAS (SEM)
PACU	142	138	45.9 (2.25)	47	47	46.0 (3.07)
0	142	139	42.0 (1.95)	47	47	42.4 (2.78)
1	142	103	39.0 (2.21)	47	36	43.8 (3.55)
2	142	101	39.3 (2.20)	47	38	41.2 (3.35)
3	142	116	36.5 (2.13)	47	37	38.0 (3.89)
4	**134**	**109**	**33.3 (2.27)**	**42**	**34**	**41.9 (4.36)**
6	118	92	29.5 (2.32)	35	29	34.9 (4.16)
8	110	84	26.5 (2.15)	28	23	30.6 (4.04)
12	110	76	28.0 (2.85)	27	22	32.5 (4.60)
16	106	83	21.5 (1.96)	26	18	27.5 (5.77)
20	103	87	20.1 (2.01)	24	17	24.0 (4.07)
24	96	88	18.5 (2.17)	23	23	19.4 (4.08)
Last observation VAS		142	30.9 (2.39)		47	40.8 (4.61)

[a]This is a modification of Table 11.2.3-6 from the study report

Overall dropout rate regardless of termination reason during the 24-hour study period
The difference in dropout rate for the intent-to-treat population was statistically significant with a p-value of 0.0162: 58/154 (38%) dropped out in the fentanyl group; 29/51 (56.9%) dropped out in the placebo group.

The difference in dropout rate for the evaluable population was also statistically significant with a p-value of 0.0107.

In a post hoc analysis of all treated patients with a PACU score of less than 75, a statistically significant treatment group difference was found with a p-value of 0.004: 38/121 dropped out in the fentanyl group; 25/45 dropped out in the placebo group.

Investigator global assessment (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. 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 this analysis, missing values were assumed to be 1 (poor).

The treatment for 102/142 (72%) evaluable patients in the fentanyl group was rated as a success as opposed to 25/47 (53%) in the placebo group (p-value, 0.018). The difference reached statistical significance in the all treated patients group (102/154, 66% in the fentanyl group vs. 25/51, 49% in the placebo group, p-value 0.028). The difference was also statistically significant in patients with a PACU score <75 (86/121, 71% in the fentanyl group vs. 22/45, 49% in the placebo group, p-value 0.008).

In a post hoc analysis of global assessment mean scores, there was a statistically significant difference when the results from all treated patients were analyzed (p-value 0.017). The comparison of the means for the evaluable patients reached statistical significance with a p-value of 0.007. The comparison of the means for treated patients with PACU pain <75 was statistically significant with a p-value of 0.004.

Patient global assessment (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 in 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 this analysis, missing values were assumed to be 1(poor).

While 96/142 evaluable patients in the fentanyl group rated their treatment as a success as opposed to 25/47 in the placebo group (p-value, 0.074), the difference was only statistically significant in patients with a PACU score <75 (82/121 in the fentanyl group vs. 22/45 in the placebo group, p-value 0.025).The difference did not reach statistical significance in the all treated patients group (96/154 in the fentanyl group vs. 25/51 in the placebo group, p-value 0.094).

In a post hoc analysis of patient global assessment mean scores, there was still no statistically significant difference when the results from all treated patients were analyzed. The comparison of the means for the evaluable patients reached statistical significance with a p-value of 0.0474. The comparison of the means for treated patients with PACU pain <75 was statistically significant with a p-value of 0.0269.

Assessment of the adherence of the E-TRANS system
More than 90% of patients had adherence of at least 90% of the system area without unattached edges for the entire study.

Three of the E-TRANS fentanyl systems fell off during the study. Two of these patients had back-up systems, which were supplied as part of the randomized drug pack, applied (316, 405). The third patient's system fell off during a shower. When it was reapplied, it appeared to be malfunctioning so it was returned to ALZA. The patient (1024) declined use of a second system and withdrew from the study.

Reviewer's conclusions from the efficacy results in study C-2000-008

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. Fifty-four patients withdrew from the study because of inadequate pain control after the first three hours on study: 36 of the 142 evaluable patients in the E-TRANS fentanyl group (25%) and 19 of the 47 evaluable patients in the E-TRANS placebo group (40%). The difference in dropout rate was statistically significant with a p-value of 0.0486.

Six patients received prohibited analgesics while on study: 4 in the active group and 2 in the placebo group. When statistical analyses were done omitting these patients as protocol violations, the p-value for withdrawal due to inadequate pain relief in all treated patients changed from 0.07 to 0.1.

If one looks at the percentage of dropouts in each treatment group who discontinued after 3 hours but before 24 hours due to inadequate analgesia-there is no difference. Of the 46 patients in the E-TRANS fentanyl group who discontinued prior to 24 hours of system use, 36 (78%) discontinued due to inadequate pain control after the first three hours. Of the 25 patients in the E-TRANS placebo group who discontinued prior to 24 hours of system use, 19 (76%) discontinued due to inadequate pain control after the first three hours. I would argue that if an equal percentage of patients drop out of each treatment arm due to inadequate analgesia, the trial has failed to show a benefit from use of active drug.

In the planned secondary analysis of all treated patients (n=205), 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. This result is consistent

with the conclusion drawn from my analysis of the primary efficacy measurement, the trial did not show a benefit from use of active drug.

The inclusion of patients who were not comfortable in the PACU may have played a role in this trial's failure to show benefit of active drug over placebo. As part of a posthoc analysis, ALZA introduced a variable for PACU pain score <75 or ≥75. The majority of the treated patients with PACU scores ≥75 were in the E-TRANS fentanyl group: 12% (6/51) of the patients in the placebo group had a PACU score ≥75; 21% (33/154) of the patients in the E-TRANS fentanyl group had a PACU score ≥75. In ALZA's posthoc analysis of all treated patients with a PACU score of less than 75, a statistically significant treatment group difference was found with a p-value of 0.014: 30/121 dropped out in the fentanyl group; 20/45 dropped out in the placebo group.

If one examines the patients with PACU scores under 75 who discontinued in each group to determine what percentage of the group left the study due to inadequate analgesia after 3 hours, i.e. use the number of patients who discontinued as the denominator and the number who discontinued for inadequate analgesia as the numerator, a difference is apparent. In the E-TRANS group, 24/38 discontinued for inadequate analgesia after 3 hours on study, 63%. In the placebo group, 18/25 discontinued for inadequate analgesia after 3 hours on study, 72%. 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 failed to show benefit of the active drug as compared to placebo using the predefined primary efficacy measure due to inappropriate inclusion of patients who did not meet the inclusion criteria. However, in the sub-population of patients who had been appropriately titrated to comfort before beginning use of E-TRANS fentanyl, i.e. those with a PACU score less than 75, the product demonstrated effectiveness when compared to placebo. 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-2001-011

Title:

The safety and efficacy of electrotransport (E-TRANS) fentanyl 40 mcg for the treatment of postoperative pain: A double-blind, multi-center, placebo-controlled trial incorporating JCAHO pain management standards.

Objective:

- Compare the safety and efficacy of the E-TRANS fentanyl system with the E-TRANS placebo system in the management of the first 24 hours of post-operative pain

Population:

Four hundred eighty-four adult patients were randomized to treatment with 244 receiving active drug and 240 receiving placebo.

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 (PACU) 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
- Patients with a pain score less than 5/10 five minutes after deep breathing and coughing

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 before 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

Study design:
A multi-center, double-blind, placebo-controlled, parallel-group study conducted in the Unites States of America.

Study duration:
24 hours per participant

Study procedure:
This study incorporated principles from the JCAHO Pain Management Standards which was released shortly prior to study initiation.

After surgery patients were taken to the PACU, where they were to receive titration with IV opioids if needed. The protocol specified that if the total IV opioid requirement approached 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.

After a patient had been awake, alert and comfortable *(emphasis was provided in the protocol)* in the PACU for at least 30 minutes (i.e. able to breath deeply, cough and participate in post-operative manuevers as clinically appropriate with satisfactory pain control), he/she was to be assessed for pain and provide a PACU pain score. The patient was also asked to reflect on his/her pre-operative pain management goal at this time.

If the PACU pain score was less than 5 and the rest of the entry criteria were met, patients were eligible for study participation and so were to be randomized to receive either E-TRANS fentanyl or E-TRANS placebo for the next 24 hours. Baseline assessments of pain intensity, vital signs and oxygen saturation were to be done, Hour 0.

The assigned treatment system was to be applied immediately after the Hour 0 assessment. The application site was to be wiped with an alcohol swab and then to be allowed to dry prior to application of the E-TRANS system. 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 was to be allowed as rescue medication during the first three hours after study system application.