CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-338

STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

STABILITY STUDIES

NDA:	21-338
Name of drug:	E-TRANS (fentanyl HCl) Systems
Applicant:	Alza Corporation
Documents reviewed:	\\Cdsesub1\n21338\N_000\2004-04-16\cmc \\Cdsesub1\n21338\N_000\2004-06-04\cmc \\Cdsesub1\n21338\N_000\2004-06-11
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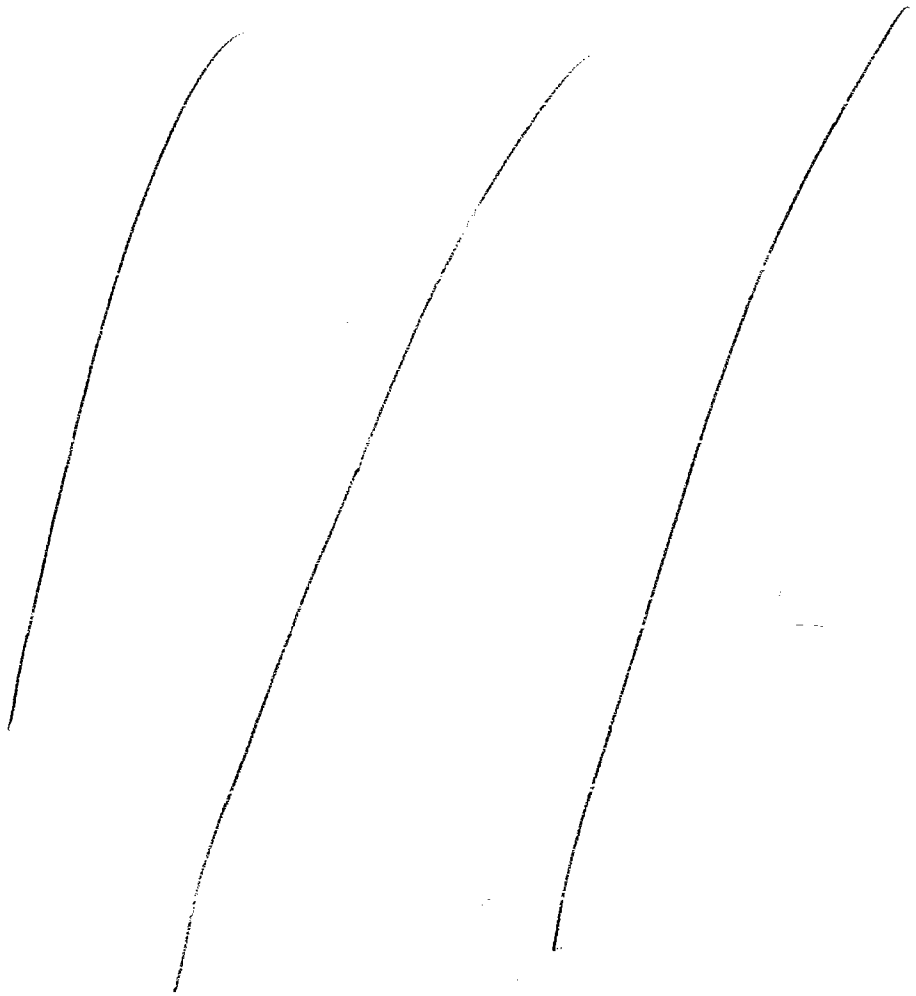
Keywords: NDA review, stability studies

I. Introduction:

The applicant, ALZA Corporation, submitted the stability data for E-TRANS (fentanyl HCl) systems to support its proposed [redacted] shelf life. The E-TRANS system is an integrated on-demand electro-transport transdermal system for patient-controlled analgesia (PCA). The system is formulated using fentanly hydrochloride, a Schedule II controlled substance, as the active ingredient in the anode hydrogel. The E-TRANS (fentanyl HCl) systems provide a nominal 40 µg dose of fentanyl (base equivalent) per activation, which is delivered over a 10-minute period with a current of 170 µA. The system is fully disposable.



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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21-338
Drug Name:	E-Trans (fentanyl HCl)
Indication(s):	Acute pain requiring opioid analgesia
Applicant:	Alza Corp.
Date(s):	Electronic NDA dated September 26, 2003
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II (HFD-715)
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Keywords: clinical study, placebo-controlled

Table of Contents

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The sponsor has submitted three placebo-controlled studies (C-2001-011, C-2000-008, and C-95-016) and one active-controlled study (C-2000-007) for the claim.

Study C-2001-011 showed that for the primary efficacy endpoint, the proportion of dropouts for inadequate pain relief, the E-TRANS (fentanyl) treated group was statistically significantly better than the placebo treatment group for both evaluable and treated patient populations. Furthermore, the treatment difference in favor of E-TRANS (fentanyl) was consistent across center, gender, age (<65 vs. ≥65) and ASA. For the secondary efficacy endpoints, E-TRANS (fentanyl) was superior to placebo for dropout for any reason, pain intensity, patient global assessment and investigator global assessment for both evaluable and treated patient populations. A treatment difference in terms of proportion of patients requiring rescue medication was observed for the treated patient population but not for the evaluable patient population.

In Study C-2000-008, for the primary efficacy endpoint, the proportion of dropouts for inadequate pain relief, E-TRANS (fentanyl) treated group was marginally statistically significantly better than the placebo treatment group for evaluable patient population, but the treatment difference failed to reach statistical significance for the treated patient population. Furthermore, the sponsor's finding from this study might not be robust. The treatment difference in favor of E-TRANS (fentanyl) was not internally consistent across center, gender, and age (<65 vs. ≥65). For the secondary efficacy endpoints, E-TRANS (fentanyl) was superior to placebo for dropout for any reason for both evaluable and treated patient populations. But for other secondary efficacy endpoints-pain intensity, patient global assessment, investigator global assessment and proportion of patients requiring rescue medication no statistically significant difference between E-TRANS (fentanyl) and placebo was shown for either evaluable patient population or treated patient population.

In study C-95-016, dominated by female patients (83%), for the primary efficacy endpoint, the proportion of dropouts for inadequate pain relief, E-TRANS (fentanyl) treated group was statistically significantly better than the placebo treatment group for both evaluable and treated patient populations. Furthermore, treatment difference in favor of E-TRANS (fentanyl) was consistent across gender, age (<65 vs. ≥65) and surgery type. For the secondary efficacy endpoints, E-TRANS (fentanyl) was superior to placebo for dropout for any reason, pain intensity, patient global assessment and investigator global assessment for both evaluable and treated patient populations. No treatment difference in terms of proportion of patients requiring rescue medication was observed for either evaluable patient population or treated patient population.

Study C-2000-007 was an open-label, randomized, active-controlled, parallel group study comparing E-TRANS (fentanyl) and IV PCA morphine treatment.

The equivalence margin of 10% was arbitrary without justification.

In this study, for the primary efficacy endpoint, the first 24-hour patient global assessment, the lower limit of the 95% confidence interval of treatment difference (fentanyl – IV PCA) was just slightly greater than -10%, the pre-specified equivalence margin from the sponsor's analysis. But from this reviewer's analysis which included 9 additional patients (3 E-TRANS (fentanyl) treated patients and 6 IV PCA morphine treated patients) who did not have patient global assessment score and these patients were considered as "success", the lower limit of 95% confidence interval of the treatment difference in success rate was just slightly less than -10%, the pre-specified equivalence margin for both evaluable and treated patient populations.

Furthermore, the lower limit of 95% confidence interval of treatment difference might be too large to make conclusion that E-TRANS (fentanyl) treatment is therapeutically equivalent to an IV PCA morphine regimen.

In conclusion, Study C-2001-011 showed superiority of the E-TRANS (fentanyl) compared to placebo. The results have been replicated in the Study C-95-016.

1.2 Brief Overview of Clinical Studies

1.2.1 Study C-2001-011

This is a double-blind, multicenter (20 sites), placebo-controlled trial to evaluate the safety and efficacy of E-TRANS (fentanyl HCl) 40 μg compared to E-TRANS (placebo) during the first 24 hours of acute moderate to severe post-operative pain requiring opioid analgesia.

After recovery from general or regional anesthesia for major abdominal, orthopedic, or thoracic surgery, the patients were titrated to comfort (pain intensity <5) with an IV opioid before enrollment. If the patient met all study screening and entry criteria, pain management was initiated with the randomly assigned E-TRANS treatment (active or placebo). The patient received his/her randomized treatment for 24 hours. Rescue medication (IV fentanyl) was available during the first 3 hours of study participation.

E-TRANS (fentanyl): 40 μg per on-demand dose, each delivered over 10 minutes for a maximum of 6 doses/hr (240 μg/hr) for 24 hours or a maximum of 80 doses (3.2 mg). Each system inactivated at 80 doses or 24 hours, whichever occurred first.

E-TRANS (placebo): Identical to E-TRANS (fentanyl HCl) 40 μg but cannot be activated to deliver drug.

Over the 24 hour treatment period, the patient was assessed periodically for pain.

The primary efficacy measurement was the number of patients in each treatment group who terminated from the study due to inadequate analgesia. This was defined as patients

with inadequate pain control three or more hours after application of the E-TRANS (fentanyl HCl) 40 μg system and who therefore required termination from the study.

Additional efficacy measurement included:

Pain Intensity: Pain intensity was measured on a verbal numerical rating scale, 0 to 10, where 0 means no pain and 10 means the worst possible pain. The pain assessment was repeated at 1-, 2-, 3-, 4-, 6-, 8-hour, and every 4 hours thereafter through the remainder of the study. If the patient was withdrawn from the study prior to the 24-hour time point, a pain assessment was completed at the time of withdrawal.

Patient Global Assessment: The patient global assessment was obtained at the time the E-TRANS treatment was terminated, either at the 24-hour time point or at the time of withdrawal. The assessment consisted of a categorical evaluation (poor, fair, good and excellent) of the E-TRANS method pain control.

Investigator Global Assessment: Investigator global assessments of the method of pain control (poor, fair, good and excellent) were obtained at the E-TRANS treatment was terminated. If the patient was withdrawn from the study prior to the 24-hour time point, the investigator global assessment was completed at the time of withdrawal.

A patient was consider to be evaluable if she/he received at least 3 hours of treatment with E-TRANS (fentanyl HCl) 40 μg or E-TRANS (placebo).

The chi-square test was used to compare the dropout rate due to inadequate pain relief during the 24-hour treatment period.

The chi-square test was used for the analysis of the overall dropout rate regardless of termination reason during the 24-hour treatment period.

A two-sample t-test was used to determine if the last pain intensity was significantly different for two treatments.

The analysis of variance was used to analyze Patient Global Assessment (PGA) and Investigator Global Assessment (IGA) data. In addition, the chi-square test was employed for the analysis of the dichotomous PGA and IGA data (good/excellent and otherwise).

If a patient was withdrawn from the study prior to the 24-hour time point, the patient and investigator global assessment was completed at the time of withdrawal. The value was used in a last observation carried forward (LOCF) analysis. For pain intensity measurement, if the patient was withdrawn before any of the suggested time points the measurement at the time of withdrawal was used for that particular time point. The numerical rating score was considered missing at any time the patient was asleep.

The primary hypothesis to be tested in this study was that there was no difference in the dropout rate due to inadequate pain relief between the E-TRANS (fentanyl HCl) 40 μg treatment group and the E-TRANS (placebo) treatment group during the 24-hour period.

All statistical tests for the efficacy analyses were performed at α=0.05 significance level. The statistical tests used for the analysis of baseline data were at a level of significance of 0.10. All tests were two-tailed.

A sample size of 430 evaluable post-operative patients randomized in a one to one ratio [215 in the E-TRANS (fentanyl HCl) treatment group and 215 in the E-TRANS (placebo) treatment group] was planned for the study. The dropout rate for inadequate analgesia was assumed to be 40% for the E-TRANS (placebo) group and 25% for the E-TRANS (fentanyl HCl) group. This sample size of 430 evaluable patients provided approximately 90% power to detect a 15% difference in the dropout rate due to inadequate analgesia during the 24-hour treatment period between the E-TRANS (fentanyl) treatment group and the E-TRANS (placebo) group at a level of significance of 5%.

To allow for 10% dropout rate prior to patients becoming evaluable, an enrollment of up to 474 patients [237 in the E-TRANS (fentanyl HCl) group and 237 in the E-TRANS (placebo) group] was planned for this study.

Of the 630 patients screened, 484 patients were randomized in E-TRANS (fentanyl) or E-TRANS (placebo) [244 in E-TRANS (fentanyl) and 240 in E-TRANS (placebo)].

A total of 439 patients [235 in E-TRANS (fentanyl) and 204 in E-TRANS (placebo)] received at least 3 hours of E-TRANS treatment were considered evaluable.

1.2.2 Study C-2000-008

This is a double-blind, multicenter (10 sites), placebo-controlled trial to evaluate the safety and efficacy of E-TRANS (fentanyl HCl) 40 μg compared to E-TRANS (placebo) during the first 24 hours of acute moderate to severe post-operative pain requiring opioid analgesia.

After recovery from general or regional anesthesia, some patients might require titration to an acceptable level of comfort using iv doses of morphine, fentanyl, sufentanil, or alfentanil. If they met the entry criteria, patients were randomized in a 3:1 ratio to E-TRANS (fentanyl): E-TRANS (placebo). Analgesia was then supplied by E-TRANS (fentanyl) or E-TRANS (placebo) for up to 24 hours. Rescue medication (IV fentanyl) was available during the first 3 hours of study participation.

All patients continued to participate in the study for either 24 hours or until one of following occurred, whichever occurred first:

- the patient's analgesia was judged to be inadequate;
- the second E-TRANS system provided as a replacement system was suspected of having a technical failure;

- any of the reasons for withdrawal.

E-TRANS (fentanyl): 40 μg per on-demand dose, each delivered over 10 minutes for a maximum of 6 doses/hr (240 μg/hr) for 24 hours or a maximum of 80 doses (3.2 mg). Each system inactivated at 80 doses or 24 hours, whichever occurred first.

E-TRANS (placebo): Identical to E-TRANS (fentanyl HCl) 40 μg but cannot be activated to deliver drug.

Over the 24 hour treatment period, the patient was assessed periodically for pain.

The primary efficacy measurement was the number of patients in each treatment group who terminated from the study due to inadequate efficacy. This was defined as patients whose pain control was judged by the investigator's staff to be inadequate after more than three hours of the E-TRANS system applications and who therefore required termination from the study.

Additional efficacy measurement included:

Pain Intensity: Pain intensity was measured on a 100-mm ungraded visual analog scale (VAS) that ranges from "no pain" (0 mm) to "worst possible pain" (100 mm). The measurement was made after the patient had been in the PACU at least 30 minutes and was awake, alert, and comfortable. The next measurements was made immediately before the E-TRANS system was initiated (Hour 0), at the 0.5-, 1-, 2-, 3-, 4-, 6-, 8-hour assessment times, and every 4 hours thereafter through the remainder of the study. If the patient was withdrawn from the study prior to the 24-hour time point, a pain assessment was completed at the time of withdrawal.

Patient Global Assessment: The patient global assessment was obtained at the time the E-TRANS treatment was terminated, either at the 24-hour time point or at the time of withdrawal. The assessment consisted of a categorical evaluation (poor, fair, good and excellent) of the E-TRANS method pain control.

Investigator Global Assessment: Investigator global assessment of the method of pain control (poor, fair, good and excellent) was obtained at the time the E-TRANS treatment was terminated. If the patient was withdrawn from the study prior to the 24-hour time point, the investigator global assessment was completed at the time of withdrawal.

A patient was considered to be evaluable if she/he received at least 3 hours of treatment with E-TRANS (fentanyl HCl) 40 μg or E-TRANS (placebo).

The chi-square test was used to compare the dropout rate due to inadequate pain relief during the 24-hour treatment period.

The chi-square test was used for the analysis of the overall dropout rate regardless of termination reason during the 24-hour treatment period.

The pain intensity was analyzed in two parts. An analysis was conducted for the 3 hours after Hour 0 when the study medication might be augmented with rescue medication to provide pain relief. A second analysis was conducted for the remaining 24 hours. A two-sample t-test was used to determine if the last pain intensity was significantly different for two treatments.

The chi-square test was employed for the analysis of the dichotomous PGA and IGA data (good/excellent and otherwise). In addition, the chi-square test was used for the analysis of the four-point categorical scales PGA and IGA data.

The primary hypothesis to be tested in this study was that there was no difference in the dropout rate due to inadequate pain relief between the E-TRANS (fentanyl HCl) 40 μg treatment group and the E-TRANS (placebo) treatment group during the 24-hour period.

All statistical tests for the efficacy analyses were performed at α=0.05 significance level. The statistical tests used for the analysis of baseline data were at a level of significance of 0.10. All tests were two-tailed.

A sample size of 164 evaluable post-operative patients randomized in a three to one ratio [123 in the E-TRANS (fentanyl HCl) treatment group and 41 in the E-TRANS (placebo) treatment group] was planned for the study. The dropout rate for inadequate analgesia was assumed to be 60% for the E-TRANS (placebo) group and 30% for the E-TRANS (fentanyl HCl) group. This sample size of 164 evaluable patients provided approximately 90% power to detect a 30% difference in the dropout rate due to inadequate analgesia during the 24-hour treatment period between the E-TRANS (fentanyl) treatment group and the E-TRANS (placebo) group at a level of significance of 5%.

To allow for 30% dropout rate prior to patients becoming evaluable, an enrollment of up to 216 patients was planned for this study.

Of the 232 patients screened, 205 were randomized in a 3:1 fashion to E-TRANS (fentanyl) or E-TRANS (placebo) [154 E-TRANS (fentanyl), 51 E-TRANS (placebo)].

A total of 189 patients [142 E-TRANS (fentanyl), 47 E-TRANS(placebo)] received at least 3 hours of treatment and were considered evaluable.

1.2.3 C-95-016

This is a single-center, randomized, double-blind, placebo-controlled, parallel-group trial to evaluate the safety and efficacy of E-TRANS (fentanyl HCl) for the treatment of postoperative pain.

The primary objective of this trial was to compare the safety and efficacy of the E-TRAN (fentanyl HCl) system versus the E-TRANS (placebo) system in the management of the first 24 hours of postoperative pain.

After recovery from general or regional anesthesia, patients were titrated to an acceptable level of comfort using iv doses of morphine, fentanyl, sufentanil, or alfentanil. If they met the entry criteria, patients were randomized in a 3:1 ratio to E-TRANS (fentanyl): E-TRANS (placebo). Analgesia was then supplied by E-TRANS (fentanyl) or E-TRANS (placebo) for up to 24 hours.

All patients continued to participate in the study for either 24 hours or until one of following occurred, whichever occurred first:

- 80 on-demand doses had been delivered from the E-TRANS system applied to the patient;
- the patient's pain control was judged to be inadequate;
- the E-TRANS system was suspected of having a technical failure;
- any of the reasons for withdrawal.

The primary efficacy measurement was the number of patients in each treatment group who dropped out of the study due to insufficient efficacy (i.e., patients whose pain control was judged by the investigator's staff to be inadequate more than three hours after E-TRANS (fentanyl) or E-TRANS (placebo) treatment had been initiated and who therefore required termination from the study).

Secondary efficacy measurement included:

Pain Intensity: Pain intensity was measured on a 100-mm ungraded visual analog scale (VAS) that ranges from "no pain" (0) to "worst possible pain" (100). The pain assessment was made immediately before titration with iv opioids; immediately before the E-TRANS (fentanyl) or E-TRANS (placebo) treatment was initiated; at 0.5, 1-, 2-, 3-, 4-, 6-, 8-hour, and every 4 hours thereafter through the remainder of the study.

Patient Global Assessment: The patient global assessment was obtained at the time the E-TRANS treatment was terminated. The assessment consisted of a categorical evaluation (poor, fair, good and excellent) of the E-TRANS method pain control. If the patient was withdrawn from the study prior to the 24-hour time point, the patient global assessment was completed at the time of withdrawal.

Investigator Global Assessment: Investigator global assessments of the method of pain control (poor, fair, good and excellent) was obtained at the E-TRANS treatment was terminated. If the patient was withdrawn from the study prior to the 24-hour time point, the investigator global assessment was completed at the time of withdrawal.

Primary efficacy parameter was withdrawal from the trial $\geq$3 hours after system application because of inadequate pain control. Other efficacy parameters were withdrawal from the trial for any reason, patient assessment of pain intensity (using a VAS of 0 to 100), and patient and investigator global assessments.

Patients who were withdrawn within the first three hours after initiation of E-TRANS treatment were replaced until 72 evaluable patients were enrolled in the E-TRANS (fentanyl) treatment group and 24 evaluable patients in the E-TRANS (placebo) treatment group.

A two sample test based on the proportion was used for the analysis of the primary efficacy parameter.

An event rate, dropout rate due to insufficient efficacy, of 70% for the E-TRANS (placebo) control group during the 24-hour E-TRANS treatment period was assumed. The sample size of 96 patients, with three-to-one enrollment ratio (72 patients in the E-TRANS (fentanyl) treatment group and 24 patients in the E-TRANS (placebo) treatment group) provided 90% power to detect a 40% event rate difference during the 24-hour treatment period between the E-TRANS (fentanyl) treatment group and the E-TRANS (placebo) control group at a significance level of α=0.05.

To allow for a 10% dropout rate prior to the patients becoming evaluable, an enrollment of up 108 patients for this study was planned.

Two sample test based on the proportion was used for the analysis of the secondary efficacy parameters (1) overall dropout rate regardless of termination reason during the 24-hour treatment period, and (5) proportion of patients requiring retitration to comfort within the first three hours after treatment initiation.

A two sample t-test was used for analysis of the numerical secondary efficacy parameters.

A two sample test based on the proportion was employed for the analysis of the dichotomous patient and investigator global assessment data (good/excellent and otherwise). In addition, the Cochran-Mantel-Haenszel (CMH) method with integer score for the test of mean scores difference was used for the analysis of the four-point categorical scale patient and investigator global assessment data.

A total of 102 patients in New Zealand were enrolled into this study. Seventy seven (77) patients were randomized to receive E-TRANS (fentanyl); 25 patients were randomized to receive E-TRANS (placebo).

Of the 102 treated patients, 21 patients [9 E-TRANS (fentanyl), 12 E-TRANS (placebo)] discontinued the study early. A total of 81 patients [68 E-TRANS (fentanyl), 13 E-TRANS (placebo)] were considered study completers having either completed the 24-hour treatment period or having used the 80-doses available before 24 hours. A total of 99 patients [77 E-TRANS (fentanyl), 22 E-TRANS (placebo)] received at least 3 hours of treatment and were considered evaluable.

1.2.4 C-2000-007

This is a multicenter (33 sites), open-label, randomized, active-controlled, parallel-group study designed to evaluate the safety and efficacy of E-TRANS (fentanyl) treatments compared to IV PCA morphine treatment for the management of acute moderate to severe post-operative pain requiring opioid analgesia for up to 3 consecutive days (72 hours).

The objective of this study was to compare the safety and efficacy of E-TRANS (fentanyl) treatment with IV PCA morphine treatment for the management of post-operative pain.

Within each of the two strata defined by surgery type, the patient was randomized equally into one of two treatment groups: E-TRANS (fentanyl) or IV PCA morphine.

After recovery from general or regional anesthesia, some patients might require titration to an acceptable level of comfort using iv doses of morphine, fentanyl, sufentanil, or alfentanil. If they met the entry criteria, patients were randomized in a 1:1 ratio to E-TRANS (fentanyl): IV PC morphine. If the patient continued to require parenteral opioid after 24 hours, the patient might continue to use E-TRANS (fentanyl) or IV PCA morphine for up to two additional 24-hour treatment periods.

The E-TRANS (fentanyl) system was removed at the end of each 24-hour treatment period and a new system was replaced at a different location on patient's chest or upper arm.

At each 24-hour assessment point, the patient and the investigator completed global assessments. If the patient was withdrawn from the study prior to any 24-hour time point, the pain intensity measurement and global assessments were completed at the time of withdrawal.

The primary efficacy measurement was the patient global assessment collected at the 24-hour time point. If the patient was withdrawn from the study prior to the 24-hour time point, the patient global assessment was completed at the time of withdrawal. The assessment consisted of a categorical evaluation (poor, fair, good and excellent) of the method of pain control.

Secondary efficacy measurement included:

Patient Global Assessments: Patient global assessments was collected at the 48- and 72 hour time points for patients who remained in the study.

Pain Intensity: Pain intensity was measured on a 100-mm ungraded visual analog scale (VAS) that ranges from "no pain" (0) to "worst possible pain" (100). The pain assessment was made immediately before the E-TRANS (fentanyl) or IV PCA morphine

treatment was initiated (Hour 0); at 0.5-, 1-, 2-, 3-, 4-, 6-, 8-hour, and every 4 hours thereafter through the remainder of the study.

Investigator Global Assessment: Investigator global assessments of the method of pain control (poor, fair, good and excellent) was obtained at the 24-hour time point and at the 48- and 72- hour time points for patients who remained in the study. If the patient was withdrawn from the study prior to the 24-hour time point, the investigator global assessment was completed at the time of withdrawal.

Number of Patients with Inadequate Pain Control: The number of patients in the E-TRANS (fentanyl) and the IV PCA morphine treatment groups whose pain control was judged by the investigator's staff to be inadequate more than 3 hours after Hour 0 and who were therefore withdrawn from the study was tabulated.

For the analysis of primary efficacy parameter, the two-sided 95% confidence interval of the difference in the success rate between the two treatments was constructed in the final analyses. E-TRANS (fentanyl) was considered therapeutically equivalent to IV PCA morphine if the lower boundary of the confidence interval is greater than or equal to -10%.

All data from all centers and surgery types were pooled.

The pain intensity was analyzed in two parts. An analysis was conducted for the first 3 hours after Hour 0 when the study medications might be augmented with rescue medication to provide pain relief. A second analysis was conducted for the remaining hours of the first 24-hour treatment period. A two-way analysis of variance (ANOVA) model was used for the analysis of the mean pain intensity. The ANOVA model included treatment, surgery type, and treatment-surgery type as factors. The interaction factor was not retained in the final model unless they were significant at a level of significance of 0.10. A similar two-way ANOVA model approach was used for analysis of the mean pain intensity scores for the second and third 24-hour treatment periods.

The primary efficacy analysis was the construction of a 95% confidence interval for the difference in the success rate based on the patient global assessment data between two treatment groups, E-TRANS (fentanyl) and IV PCA morphine.

All statistical tests for the efficacy analyses were performed at α=0.05 significance level. The statistical tests used for the analysis of baseline data were at a level of significance of 0.10. All tests were two-tailed.

A sample size of 504 evaluable patients (252 patients in each treatment group) was planned for this study. The sample size provided 80% power to demonstrate the therapeutic equivalence in proportion between two treatments.

Two treatments was considered therapeutically equivalent if the 95% confidence interval of the difference in success rate falls within ±10% based on two one-sided tests with α=0.025 and a maximum acceptance difference of 10%.

Assuming a success rate of 80% for both E-TRANS (fentanyl) and the IV PCA morphine treatment groups, a sample size of 252 patients was needed for each treatment group (Makuch and Simon, 1978).

To allow for a 20% dropout rate prior to the patient becoming evaluable, an enrollment of up to 630 patients for this was planned.

Of the 726 patients screened, 636 were randomized to E-TRANS (fentanyl) or IV PCA morphine pump applied (316 E-TRANS (fentanyl), 320 IV PCA morphine).

A total of 626 patients (310 E-TRANS (fentanyl), 316 IV PCA morphine) who received at least 3 hours of treatment and completed a patient global assessment were considered evaluable.

1.3 Statistical Issues and Finding

The sponsor has submitted three placebo-controlled studies (C-2001-011, C-2000-008, and C-95-016) and one active-controlled study (C-2000-007) for the claim.

Study C-2001-011 showed that for the primary efficacy endpoint, the proportion of dropouts for inadequate pain relief, E-TRANS (fentanyl) treated group was statistically significantly better than the placebo treatment group for both evaluable and treated patient populations. Furthermore, treatment difference in favor of E-TRANS (fentanyl) was consistent across center, gender, age (<65 vs. ≥65) and ASA. For the secondary efficacy endpoints, the E-TRANS (fentanyl) was superior to placebo for dropout for any reason, pain intensity, patient global assessment and investigator global assessment for both evaluable and treated patients populations. Treatment difference in terms of proportion of patients requiring rescue medication was observed for treated patient population but not for evaluable patient population.

In Study C-2000-08, for the primary efficacy endpoint, the proportion of dropouts for inadequate pain relief, E-TRANS (fentanyl) treated group was marginally statistically significantly better than the placebo treatment group for evaluable patient population, but the treatment difference failed to reach statistical significance for treated patient population. Furthermore, the sponsor's finding from this study might not be robust. The treatment difference in favor of E-TRANS (fentanyl) was not internally consistent across center, gender, and age (<65 vs. ≥65). For the secondary efficacy endpoints, the E-TRANS (fentanyl) was superior to placebo for dropout for any reason for both evaluable and treated patient populations. But for other secondary efficacy endpoints: pain intensity, patient global assessment, investigator global assessment and proportion of patients requiring rescue medication, no statistically significant difference between

E-TRANS (fentanyl) and placebo was shown for either evaluable patient population or treated patient population.

Study C-95-016, dominated by females (83%), showed that for the primary efficacy endpoint, the proportion of dropouts for inadequate pain relief, E-TRANS (fentanyl) treated group was statistically significantly better than the placebo treatment group for both evaluable and treated patient populations. Furthermore, treatment difference in favor of E-TRANS (fentanyl) was consistent across gender, age (<65 vs. ≥65) and surgery type. For the secondary efficacy endpoints, the E-TRANS (fentanyl) was superior to placebo for dropout for any reason, pain intensity, patient global assessment and investigator global assessment for both evaluable and treated patients populations. No Treatment difference in terms of proportion of patients requiring rescue medication was observed for either evaluable patient population or treated patient population.

Study C-2000-07 was an open-label, randomized, active-controlled, parallel group study comparing E-TRANS (fentanyl) and IV PVA morphine treatment.

The equivalence margin of 10% was arbitrary without justification.

This study showed that for the primary efficacy endpoint, the first 24-hour patient global assessment, the lower limit of the 95 confidence interval of treatment difference (fentanyl – IV PCA) was just slightly greater than -10%, the pre-specified equivalence margin from the sponsor's analysis. But from this reviewer's analysis which included 9 additional patients (3 E-TRANS (fentanyl) treated patients and 6 IV PCA morphine treated patients) who did not have patient global assessment score and these patients were considered as "success", the lower limit of 95% confidence interval of the treatment difference in success rate was just slightly less than -10%, the pre-specified equivalence marginal for both evaluable and treated patient populations.

Furthermore, the lower limit of 95% confidence interval of treatment difference might be too large to make conclusion that E-TRANS (fentanyl) treatment is therapeutically equivalent to an IV PCA morphine regimen.

2. INTRODUCTION

2.1 Overview

The E-TRANS (fentanyl HCl) system is a patient-controlled transdermal delivery system designed to provide on-demand of fentanyl through intact skin by user's activation of a single output constant current source.

In the current NDA, the sponsor seeks approval of an E-TRANS (fentanyl HCl) fentanyl system that delivers a nominal 40 μg on-demand dose for treatment of acute pain that requires opioid analgesia in adult patients.

2.2 Data Sources

The sponsor has submitted three placebo-controlled studies and one active-controlled study for the claim. These studies include:

C-2001-011: The Safety and Efficacy of Electrotransport E-TRANS (fentanyl HCl) 40 μg for the Treatment of Post-Operative Pain: A Double-Blind, Multicenter, Placebo-Controlled Trial Incorporating JCAHO Pain Management Standard

C-2000-008: The Safety and Efficacy of Electrotransport (E-TRANS) Fentanyl for the Treatment of Post-Operative Pain: A Double-Blind, Multicenter, Placebo-Controlled Trial

C-95-016: The Safety and Efficacy of Electrotransport (E-TRANS) Fentanyl for the Treatment of Post-Operative Pain: A Double-Blind, Multicenter, Placebo-Controlled Trial

C-2000-007: The Safety and Efficacy of Electrotransport (E-TRANS) Fentanyl Compared to IV PCA Morphine for the Treatment of Post-Operative Pain

All data were submitted in electronic format to the EDR.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study C-2001-011

3.1.1.1 Study Design

This is a double-blind, multicenter (20 sites), placebo-controlled trial to evaluate the safety and efficacy of E-TRANS (fentanyl HCl) 40 μg compared to E-TRANS(placebo) during the first 24 hours of acute moderate to severe post-operative pain requiring opioid analgesia.

After recovery from general or regional anesthesia for major abdominal, orthopedic, or thoracic surgery, the patients were titrated to comfort (pain intensity <5) with an IV opioid before enrollment. If the patient met all study screening and entry criteria, pain management was initiated with the randomly assigned E-TRANS treatment (active or placebo). The patient received his/her randomized treatment for 24 hours. Rescue medication (IV fentanyl) was available during the first 3 hours of study participation.

E-TRANS (fentanyl): 40 μg per on-demand dose, each delivered over 10 minutes for a maximum of 6 doses/hr (240 μg/hr) for 24 hours or a maximum of 80 doses (3.2 mg). Each system inactivated at 80 doses or 24 hours, whichever occurred first.

E-TRANS (placebo): Identical to E-TRANS (fentanyl HCl) 40 μg but cannot be activated to deliver drug.

Over the 24 hour treatment period, the patient was assessed periodically for pain.

The primary efficacy measurement was the number of patients in each treatment group who terminated from the study due to inadequate analgesia. This was defined as patients with inadequate pain control three or more hours after application of the E-TRANS (fentanyl HCl) 40 μg system and who therefore required termination from the study.

Additional efficacy measurement included:

Pain Intensity: Pain intensity was measured on a verbal numerical rating scale, 0 to 10, where 0 means no pain and 10 means the worst possible pain. The pain assessment was repeated at 1-, 2-, 3-, 4-, 6-, 8-hour, and every 4 hours thereafter through the remainder of the study. If the patient was withdrawn from the study prior to the 24-hour time point, a pain assessment was completed at the time of withdrawal.

Patient Global Assessment: The patient global assessment was obtained at the time the E-TRANS treatment was terminated, either at the 24-hour time point or at the time of withdrawal. The assessment consisted of a categorical evaluation (poor, fair, good and excellent) of the E-TRANS method pain control.

Investigator Global Assessment: Investigator global assessments of the method of pain control (poor, fair, good and excellent) were obtained at the E-TRANS treatment was terminated. If the patient was withdrawn from the study prior to the 24-hour time point, the investigator global assessment was completed at the time of withdrawal.

A patient was consider to be evaluable if she/he received at least 3 hours of treatment with E-TRANS (fentanyl HCl) 40 μg or E-TRANS (placebo).

The primary efficacy parameter was the dropout rate due to inadequate pain relief during the 24-hour treatment period. Inadequate pain relief for a patient was defined as pain control judged by the patients and the investigator's staff to be inadequate more than three hours after initiation of the treatment period (Hour 0) and requiring termination from the study.

Additional efficacy parameters were:

(1) Overall dropout rate regardless of termination reason during the 24-hour treatment period.
(2) Last pain intensity obtained during the 24-hour E-TRANS treatment period.
(3) The patient global assessment at the time of treatment termination.
(4) The investigator global assessment at the time of treatment termination.

Of the 630 patients screened, 484 patients were randomized in E-TRANS (fentanyl) or E-TRANS (placebo) (244 in fentanyl and 240 in placebo).

A total of 439 patients (235 in E-TRANS (fentanyl) and 204 in E-TRANS (placebo)) received at least 3 hours of E-TRANS treatment were considered evaluable.

3.1.1.2 Sponsor's Analysis

3.1.1.2.1 Planned Analysis

The chi-square test was used to compare the dropout rate due to inadequate pain relief during the 24-hour treatment period.

The chi-square test was used for the analysis of the overall dropout rate regardless of termination reason during the 24-hour treatment period.

A two-sample t-test was used to determine if the last pain intensity was significantly different for two treatments.

The analysis of variance was used to analyze Patient Global Assessment (PGA) and Investigator Global Assessment (IGA) data. In addition, the chi-square test was employed for the analysis of the dichotomous PGA and IGA data (good/excellent and otherwise).

If a patient was withdrawn from the study prior to the 24-hour time point, the patient and investigator global assessment was completed at the time of withdrawal. The value was used in a last observation carried forward (LOCF) analysis. For pain intensity measurement, if the patient was withdrawn before any of the suggested time points the measurement at the time of withdrawal was used for that particular time point. The numerical rating score was considered missing at any time the patient was asleep.

The primary hypothesis to be tested in this study was that there was no difference in the dropout rate due to inadequate pain relief between the E-TRANS (fentanyl HCl) 40 μg treatment group and the E-TRANS (placebo) treatment group during the 24-hour period.

All statistical tests for the efficacy analyses were performed at α=0.05 significance level. The statistical tests used for the analysis of baseline data were at a level of significance of 0.10. All tests were two-tailed.

A sample size of 430 evaluable post-operative patients randomized in a one to one ratio [215 in the E-TRANS (fentanyl HCl) treatment group and 215 in the E-TRANS (placebo) treatment group] was planned for the study. The dropout rate for inadequate analgesia was assumed to be 40% for the E-TRANS (placebo) group and 25% for the E-TRANS (fentanyl HCl) group. This sample size of 430 evaluable patients provided approximately 90% power to detect a 15% difference in the dropout rate due to inadequate analgesia during the 24-hour treatment period between the

E-TRANS (fentanyl) treatment group and the E-TRANS (placebo) group at a level of significance of 5%.

To allow for 10% dropout rate prior to patients becoming evaluable an enrollment of up to 474 patients [237 in the E-TRANS (fentanyl HCl) group and 237 in the E-TRANS (placebo) group] was planned for this study.

3.1.1.2.2 Treatment Group Comparability

Appendix Table 1 presents the demographic and baseline characteristics of all treated patients.

As seen from Appendix Table 1, the two treatment groups were similar with respect to demographic characteristics, surgery type and post-operative ASA physical status.

3.1.1.2.3 Sponsor's Analysis of Primary Efficacy Variable

The primary efficacy parameter was the dropout rate due to insufficient efficacy during the 24-hour treatment period.

The number of patients withdrew from the study prematurely because of inadequate pain control after the first 3 hours on study are given below.

Inadequate Pain Relief
(Evaluable Patients)
Study C-2001-011

Treatment	Inadequate Pain Relief	Diff (Fentanyl-Placebo)	P-value
E-TRANS (fentanyl)	64/235 (27.2%)	-29.6%	<0.0001
Placebo	116/204 (56.9%)		

Copied from Table 11.2.3-1
P-value was calculated using chi-square test for categorical data.

As seen from table above, the proportion of dropouts for inadequate pain relief was statistically significantly less for the active than the placebo treatment group.

3.1.1.2.4 Sponsor's Analysis of Secondary Efficacy Variables

3.1.1.2.4.1 Overall Dropout Rate

The number of patients withdrew from the study prematurely for any reason is given below.

Dropout for Any Reason
(Evaluable Patients)
Study C-2001-011

Treatment	For Any Reason	Diff (Fentanyl-Placebo)	P-value
E-TRANS (fentanyl)	81/235 (34.5%)	-28.3%	<0.0001
Placebo	128/204 (62.7%)		

Copied from Table 11.2.3-1
P-value was calculated using chi-square test for categorical data.

As seen from the table above, the proportion of dropouts for any reason was statistically significantly less for the active than the placebo treatment group.

3.1.1.2.4.2 Mean Pain Intensity

Mean values for pain intensity calculated by time point and by treatment group are summarized below.

Pain Intensity Scores by Time
(Evaluable Patients)

	Treatment Group					
	E-TRANS (fentanyl) 40 µg (n=235)			Placebo (n=204)		
	No. of Patients	No. of Patients with Scores	Mean (SEM)	No. of Patients	No. of Patients with Scores	Mean (SEM)
Hours post-enrollment						
0	235	235	3.0 (0.08)	204	204	3.1 (0.08)
1	235	207	3.2 (0.13)	204	180	3.5 (0.14)
2	235	200	3.4 (0.13)	204	185	3.8 (0.15)
3	235	201	3.3 (0.13)	204	181	3.9 (0.16)
4	224	191	3.4 (0.15)	176	153	3.9 (0.18)
6	195	167	3.1 (0.16)	143	124	3.8 (0.20)
8	186	157	2.8 (0.15)	125	106	3.7 (0.22)
12	179	138	2.5 (0.16)	108	81	3.4 (0.23)
16	174	147	2.4 (0.12)	97	86	3.7 (0.26)
20	165	156	2.5 (0.14)	80	76	3.3 (0.23)
24	148	148	2.1 (0.12)	66	65	3.0 (0.18)
Last observation (<0.0001)[a]	235	235	3.4 (0.16)	204	204	5.3 (0.18)

Note: Only patients with a pain intensity score at the given time point are included in the calculation of the mean.
[a] p-value for the difference between the averages of the last pain assessment for the two treatments was based on an ANOVA.

Scores for the last observation VAS were significantly lower for the active than for placebo treatment.

3.1.1.2.4.3 Patient Global Assessment

The results of patient global assessment are summarized below.

Patient Global Assessment
(Evaluable Patients)
Study C-2001-011

Assessment	(fentanyl) 40 µg	Placebo	p-value
Excellent	97 (41.3%)	34 (16.7%)	<0.0001
Good	82 (34.9%)	72 (35.3%)	
Fair	34 (14.5%)	46 (22.5%)	
Poor	22 (9.4%)	51 (25.0%)	
Missing	0	1 (0.5%)	

Copied from Table 11.2.3-7
P-value was calculated using chi-square test for categorical data.

As seen from the table above, there was significant treatment difference in favor of E-TRANS (fentanyl) in terms of patient global assessment.

3.1.1.2.4.4 Investigator Global Assessment

The results of investigator global assessment are summarized below.

Investigator Global Assessment
(Evaluable Patients)
C-2001-011

Assessment	(fentanyl) 40 µg	Placebo	p-value
Excellent	116 (49.4%)	50 (24.5%)	<0.0001
Good	60 (25.5%)	57 (27.9%)	
Fair	38 (16.2%)	59 (28.9%)	
Poor	20 (8.5%)	37 (18.1%)	
Missing	1 (0.4%)	1 (0.5)	

Copied from Table 11.2.3-9
P-value was calculated using chi-square test for categorical data.

As seen from the table above, there was significant treatment difference in favor of E-TRANS (fentanyl) in terms of investigator global assessment.

3.1.1.2.4.5 Proportion of Patients Requiring Rescue Medication

The number of patients requiring rescue medication is given below.

Patients Requiring Rescue Medication
(Evaluable Patients)
C-2001-011

Treatment	Requiring Rescue Medication	Diff (Fentanyl-Placebo)	P-value
Fentanyl	105/235 (44.7%)	-7.3%	0.1278
Placebo	106/204 (52.0%)		

Copied from Table 11.2.4-8.
P-value was calculated using chi-square test for categorical data.

As seen from the table above, there was no treatment difference in terms of proportion of patients requiring rescue medication.

3.1.1.3 Reviewer's Comments and Evaluation

3.1.1.3.1 Disproportional Number of Suspected Technical Failures

There is disproportional number of patients with suspected technical failures (15 in fentanyl, 37 in placebo; p=0.0015).

This reviewer performed analysis of primary endpoint for treated patient population adjusted for suspected technique failures status using Mantel-Haenszel's method. The results are given below.

Inadequate Pain Relief
(Treated Patients)
Study C-2001-011

Suspected Technical Failure	Fentanyl	Placebo	Difference
No	68/229 (29.7%)	123/203 (60.6%)	-30.9%
Yes	2/15 (13.3%)	21/37 (56.8%)	-43.4%

Complied by this reviewer.

P-value adjusted for suspected technique failure status was <0.0001. So, the impact of disproportional number of patients with suspected technical failure on the primary efficacy endpoint was minimum.

3.1.1.3.2 Reviewer's Comments on Sponsor's Analysis of Primary Endpoint

There were 45 patients (9 in fentanyl, 36 in placebo) were excluded from sponsor's evaluable patients analysis.

The sponsor also performed analysis of primary endpoint for treated patient population. The number of patients withdrew from the study prematurely because of inadequate pain control after the first 3 hours on study for treated patients are given below.

Inadequate Pain Relief
(Treated Patients)
Study C-2001-011

Treatment	Inadequate Pain Relief	Diff (Fentanyl-Placebo)	P-value
E-TRANS (fentanyl)	70/244 (28.7%)	-31.3%	<0.0001
Placebo	144/240 (60.0%)		

Copied from Table 11.3.3-1
P-value was calculated using chi-square test for categorical data.

As seen from the table above, the results from treated patient analysis were similar to those from sponsor's evaluable patient analysis.

3.1.1.3.2.1 Subgroup Analysis

Subgroup analyses were preformed for the primary endpoint for the subgroups: center, patients aged <65 years vs. ≥65 years; male patients vs. female patients for treated patient population.

The results of subgroup analysis of inadequate pain relief are given below.

Inadequate Pain Relief by Subgroup
(Treated Patients)
Study C-2001-011

Subgroup	E-TRANS (fentanyl)	Placebo	Difference	p-value	Breslow-Day p-value
Center					0.2846
1	1/5 (20.0%)	4/6 (66.7%)	-46.7%	0.2424	
2	3/11 (27.3%)	7/11 (63.6%)	-36.4%	0.1984	
3	0/1 (0.0%)	0/2 (0.0%)			
4	1/5 (20.0%)	4/6 (66.7%)	-46.7%	0.2424	
5	1/2 (50%)	1/1 (100%)	-50.0%	1.0000	
7	0/6 (0.0%)	4/7 (57.1%)	-57.1%	0.0699	
8	2/6 (33.3%)	2/5 (40.0%)	-6.7%	1.0000	
9	0/2 (.0%)	0/0			
10	1/17 (5.9%)	9/17 (52.9%)	-47.1%	0.0066	
11	0/3 (0.0%)	1/3 (33.3%)	-33.3%	1.0000	
12	6/12 (50.0%)	6/11 (54.5%)	-4.5%	1.0000	
13	0/5 (0.0%)	3/5 (60.0%)	-60.0%	0.1667	
14	9/27 (33.3%)	16/26 (61.5%)	-28.2%	0.0556	
15	1/3 (33.3%)	2/2 (100.0%)	-66.7%	0.4000	
16	2/13 (15.4%)	7/13 (53.8%)	-38.5%	0.0968	
17	12/27 (44.4%)	14/27 (51.9%)	-7.4%	0.7857	
18	6/27 (22.2%)	20/26 (76.9%)	-54.7%	<0.0001	
19	5/17 (29.4%)	9/16 (56.3%)	-26.8%	0.1669	
20	14/39 (35.9%)	21/39 (53.8%)	-17.9%	0.1716	
21	6/16 (37.5%)	14/17 (82.4%)	-44.9%	0.0134	
Gender					0.0675
Male	21/74 (28.4%)	44/70 (62.9%)	-34.5%	<0.0001	
Female	49/170 (28.8%)	100/170 (58.8%)	-30.0%	<0.0001	
Age					0.6527
<65	49/172 (28.5%)	120/187 (64.2%)	-35.7%	<0.0001	
≥65	21/72 (29.2%)	24/53 (45.3%)	-16.1%	0.0893	
Surgery Type					0.3372
Lower Abdominal	28/121 (23.1%)	71/115 (61.7%)	-38.6%	<0.0001	
Orthopedic	40/113 (35.4%)	69/110 (62.8%)	-27.3%	<0.0001	
Bone					
Thoracic	0/6 (0.0%)	0/7 (0.0%)	0.0%		
U. Abdominal	1/1 (100%)	1			
L. Abdominal					
ASA					0.1931
I	6/25 (24.0%)	22/80 (73.3%)	-49.3	0.0003	
II	50/175 (28.6%)	91/150 (60.7%)	-32.1	<0.0001	
III	14/44 (31.8%)	31/60 (51.7%)	-19.8	0.0435	

P-values were obtained using Fisher's exact test
Compiled by this reviewer.

As seen from the table above, treatment difference in favor of E-TRANS (fentanyl) was consistent across center, gender, age (<65 vs. ≥65) and ASA.

3.1.1.3.3 Reviewer's Comments on Sponsor's Analysis of Secondary Endpoint

The sponsor also performed analysis of patient global assessment and investigator global assessment for treated patient population. The results were similar to those for evaluable patients.

3.1.1.3.3.1 Overall Dropout Rate

Per medical officer's request, this reviewer performed analysis of over dropout rate for treated patients. The number of patients withdrew from the study prematurely for any reason is given below.

Dropout for Any Reason
(Treated Patients)
Study C-2001-011

Treatment	For Any Reason	Diff (Fentanyl-Placebo)	P-value
E-TRANS (fentanyl)	90/244 (36.9%)	-31.4%	<0.0001
Placebo	164/240 (68.3%)		

Compiled by this reviewer.
P-value was calculated using chi-square test for categorical data.

As seen from the table above, the results from treated patient analysis were similar to those from sponsor's evaluable patient analysis.

3.1.1.3.3.2 Patients Requiring Rescue Medication

The sponsor also performed analysis of patients requiring rescue medication for treated patient population.

The number of patients requiring rescue medication for treated patients is given below.

Patients Requiring Rescue Medication
(Treated Patients)
C-2001-011

Treatment	Requiring Rescue Medication	Diff (Fentanyl-Placebo)	P-value
Fentanyl	111/244 (45.5%)	-12.0%	0.0082
Placebo	138/240 (57.5%)		

Copied from Table 11.3.4-8.
P-value was calculated using chi-square test for categorical data.

As seen from the table above, contrary to the finding from sponsor's evaluable patients analysis, the treatment difference achieved statistical significance for treated patient population.

3.1.2 Study C-2000-008

3.1.2.1 Study Design

This is a double-blind, multicenter (10 sites), placebo-controlled trial to evaluate the safety and efficacy of E-TRANS (fentanyl HCl) 40 μg compared to E-TRANS (placebo) during the first 24 hours of acute moderate to severe post-operative pain requiring opioid analgesia.

After recovery from general or regional anesthesia, some patients might require titrated to an acceptable level of comfort using iv doses of morphine, fentanyl, sufentanil, or alfentanil. If they met the entry criteria, patients were randomized in a 3:1 ratio to E-TRANS (fentanyl): E-TRANS (placebo). Analgesia was then supplied by E-TRANS (fentanyl) or E-TRANS (placebo) for up to 24 hours.

All patients continued to participate in the study for either 24 hours or until one of following occurred, whichever occurred first:

- the patient's analgesia was judged to be inadequate;
- the second E-TRANS system provided as a replacement system was suspected of having a technical failure;
- any of the reasons for withdrawal.

If the patient met all study screening and entry criteria, patient was randomly in a 3:1 into E-TRANS (fentanyl): E-TRANS (placebo). The patient received his/her randomized treatment for 24 hours. Rescue medication (IV fentanyl) was available during the first 3 hours of study participation.

E-TRANS (fentanyl): 40 μg per on-demand dose, each delivered over 10 minutes for a maximum of 6 doses/hr (240 μg/hr) for 24 hours or a maximum of 80 doses (3.2 mg). Each system inactivated at 80 doses or 24 hours, whichever occurred first.

E-TRANS (placebo): Identical to E-TRANS (fentanyl HCl) 40 μg but cannot be activated to deliver drug.

Over the 24 hour treatment period, the patient was assessed periodically for pain.

The primary efficacy measurement was the number of patients in each treatment group who terminated from the study due to inadequate efficacy. This was defined as patients whose pain control was judged by the investigator's staff to be inadequate after more than three hours of the E-TRANS system applications and who therefore required termination from the study.

Additional efficacy measurement included:

Pain Intensity: Pain intensity was measured on a 100-mm ungraded visual analog scale (VAS) that ranges from "no pain" (0 mm) to "worst possible pain" (100 mm). The

measurement was made after the patient had been in the PACU at least 30 minutes and was awake, alert, and comfortable. The next measurements was made immediately before the E-TRANS system was initiated (Hour 0), at the 0.5-, 1-, 2-, 3-, 4-, 6-, 8-hour assessment times, and every 4 hours thereafter through the remainder of the study. If the patient was withdrawn from the study prior to the 24-hour time point, a pain assessment was completed at the time of withdrawal.

Patient Global Assessment: The patient global assessment was obtained at the time the E-TRANS treatment was terminated, either at the 24-hour time point or at the time of withdrawal. The assessment consisted of a categorical evaluation (poor, fair, good and excellent) of the E-TRANS method pain control.

Investigator Global Assessment: Investigator global assessments of the method of pain control (poor, fair, good and excellent) was obtained at the time the E-TRANS treatment was terminated. If the patient was withdrawn from the study prior to the 24-hour time point, the investigator global assessment was completed at the time of withdrawal.

A patient was considered to be evaluable if she/he received at least 3 hours of treatment with E-TRANS (fentanyl HCl) 40 μg or E-TRANS (placebo).

The primary efficacy parameter was the dropout rate due to inadequate pain relief during the 24-hour treatment period. Inadequate pain relief for a patient was defined as pain control judged by the investigator's staff to be inadequate more than three hours after initiation of the treatment period (Hour 0) and requiring termination from the study.

Additional efficacy parameters were:

(1) Overall dropout rate regardless of termination reason during the 24-hour treatment period.
(2) Mean pain intensity over the 24-hour E-TRANS treatment period.
(3) The patient global assessment at the time of treatment termination.
(4) The investigator global assessment at the time of treatment termination.

Of the 232 patients screened, 205 were randomized in a 3:1 fashion to E-TRANS (fentanyl) or E-TRANS (placebo) [154 E-TRANS (fentanyl), 51 E-TRAN (placebo)].

A total of 189 patients [142 E-TRANS (fentanyl), 47 E-TRANS (placebo)] received at least 3 hours of treatment and were considered evaluable.

3.1.2.2 Sponsor's Analysis

3.1.2.2.1 Planned Analysis

The chi-square test was used to compare the dropout rate due to inadequate pain relief during the 24-hour treatment period.

The chi-square test was used for the analysis of the overall dropout rate regardless of termination reason during the 24-hour treatment period.

The pain intensity was analyzed in two parts. An analysis was conducted for the 3 hours after Hour 0 when the study medication might be augmented with rescue medication to provide pain relief. A second analysis was conducted for the remaining 24 hours. A two-sample t-test was used to determine if the last pain intensity was significantly different for two treatments.

The chi-square test was employed for the analysis of the dichotomous PGA and IGA data (good/excellent and otherwise). In addition, the chi-square test was used for the analysis of the four-point categorical scales PGA and IGA data.

The primary hypothesis to be tested in this study was that there was no difference in the dropout rate due to inadequate pain relief between the E-TRANS (fentanyl HCl) 40 μg treatment group and the E-TRANS (placebo) treatment group during the 24-hour period.

All statistical tests for the efficacy analyses were performed at α=0.05 significance level. The statistical tests used for the analysis of baseline data were at a level of significance of 0.10. All tests were two-tailed.

A sample size of 164 evaluable post-operative patients randomized in a three to one ratio [123 in the E-TRANS (fentanyl HCl) treatment group and 41 in the E-TRANS (placebo) treatment group] was planned for the study. The dropout rate for inadequate analgesia was assumed to be 60% for the E-TRANS (placebo) group and 30% for the E-TRANS (fentanyl HCl) group. This sample size of 164 evaluable patients provided approximately 90% power to detect a 30% difference in the dropout rate due to inadequate analgesia during the 24-hour treatment period between the E-TRANS (fentanyl) treatment group and the E-TRANS (placebo) group at a level of significance of 5%.

To allow for 30% dropout rate prior to patients becoming evaluable an enrollment of up to 216 patients was planned for this study.

3.1.2.2.2 Treatment Group Comparability

Appendix Table 2 presents the demographic and baseline characteristics of all treated patients.

As seen from Appendix Table 2, the two treatment groups were similar with respect to demographic characteristics, surgery type and post-operative ASA physical status.

3.1.2.2.3 Sponsor's Analysis of Primary Efficacy Variable

The primary efficacy parameter was the dropout rate due to insufficient efficacy during the 24-hour treatment period.

The number of patients withdrew from the study prematurely because of inadequate pain control after the first 3 hours on study are given below.

Inadequate Pain Relief
(Evaluable Patients)
Study C-2000-008

Treatment	Inadequate Pain Relief	Diff (Fentanyl-Placebo)	P-value
Fentanyl	36/142 (25.4%)	-15.1%	0.0486
Placebo	19/47 (40.4%)		

Copied from Table 11.2.3-1
P-value was calculated using chi-square test for categorical data.

As seen from table above, the proportion of dropouts for inadequate pain relief was marginally statistically significantly less for the active than the placebo treatment group.

3.1.2.2.4 Sponsor's Analysis of Secondary Efficacy Variables

3.1.2.2.4.1 Overall Dropout Rate

The number of patients withdrew from the study prematurely for any reason is given below.

Dropout for Any Reason
(Evaluable Patients)
Study C-2000-008

Treatment	For Any Reason	Diff (Fentanyl-Placebo)	P-value
Fentanyl	46/142 (32.4%)	-20.8%	0.0107
Placebo	25/47 (53.2%)		

Copied from Table 11.2.3-1
P-value was calculated using chi-square test for categorical data.

As seen from the table above, the proportion of dropouts for any reason was statistically significantly less for the active than the placebo treatment group.

3.1.2.2.4.2 Mean Pain Intensity

Mean values for pain intensity calculated by time point and by treatment group are summarized below.

Pain Intensity VAS Scores by Time
(Evaluable Patients)

	Treatment Group					
	E-TRANS (fentanyl) 40 µg (n=142)			Placebo (n=47)		
	No. of Patients	No. of Patients with VAS Scores	Mean VAS (SEM)	No. of Patients	No. of Patients with VAS Scores	Mean VAS (SEM)
Hours post-enrollment						
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)
0.5	142	103	39.0 (2.21)	47	36	43.8 (3.55)
1	142	101	39.3 (2.20)	47	38	41.2 (3.35)
2	142	118	38.9 (2.13)	47	40	45.2 (3.69)
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 (0.0474)[a]	142	142	30.9 (2.39)	47	47	40.8 (4.61)

Note: Only patients with a pain intensity score at the given time point are included in the calculation of the mean.
[a] p-value for the difference between the averages of the last pain assessment for the two treatments was based on an ANOVA.

Scores for the last observation VAS were significantly lower for the active than for placebo treatment.

3.1.2.2.4.3 Patient Global Assessment

The results of patient global assessment are summarized below.

Patient Global Assessment
(Evaluable Patients)
Study C-2000-008

Assessment	(fentanyl) 40 µg	Placebo	p-value
Excellent	70 (49.3%)	14 (29.8%)	0.1211
Good	26 (18.3%)	11 (23.4%)	
Fair	16 (11.3%)	9 (19.1%)	
Poor	29 (20.4%)	13 (27.7%)	
Missing	1 (0.7%)	0 (0%)	

Copied from Table 11.2.3-7
P-value was calculated using chi-square test for categorical data.

As seen from the table above, there was not significant treatment difference in favor of E-TRANS (fentanyl) in terms of patient global assessment.

3.1.2.2.4.4 Investigator Global Assessment

The results of investigator global assessment are summarized below.

Investigator Global Assessment
(Evaluable Patients)
Study C-2000-008

Assessment	(fentanyl) 40 µg	Placebo	p-value
Excellent	76 (53.5%)	16 (34.0%)	0.0591
Good	26 (18.3%)	9 (19.1%)	
Fair	21 (14.8%)	9 (19.1%)	
Poor	18 (12.7%)	13 (27.7%)	
Missing	1 (0.7%)	0 (0%)	

Copied from Table 11.2.3-9
P-value was calculated using chi-square test for categorical data.

As seen from the table above, treatment difference in favor of E-TRANS(fentanyl) in terms of investigator global assessment was close to be statistical significance.

3.1.2.2.4.5 Proportion of Patients Requiring Rescue Medication

The number of patients requiring rescue medication is given below.

Patients Requiring Rescue Medication
(Evaluable Patients)
Study C-2000-008

Treatment	Requiring Rescue Medication	Diff (Fentanyl-Placebo)	P-value
Fentanyl	68/142 (47.9%)	-7.4%	0.3771
Placebo	26/47 (55.3%)		

Copied from Table 11.2.4-8.
P-value was calculated using chi-square test for categorical data.

As seen from the table above, there was no treatment difference in terms of proportion of patients requiring rescue medication.

3.1.2.3 Reviewer's Comments and Evaluation

A total of 16 patients (12 in E-TRANS (fentanyl) and 4 in placebo) were excluded in the sponsor's evaluable analysis.

3.1.2.3.1 Reviewer's Comments on Sponsor's Analysis of Primary Endpoint

The sponsor also performed analysis of the primary endpoint for treated patient population.

The number of patients withdrew from the study prematurely because of inadequate pain control after the first 3 hours on study for treated patients are given below.

Inadequate Pain Relief
(Treated Patients)
Study C-2000-008

Treatment	Inadequate Pain Relief	Diff (Fentanyl-Placebo)	P-value
E-TRANS(fentanyl)	48/154 (31.2%)	-13.9%	0.0700
Placebo	23/51 (45.1%)		

Copied from Table 11.3.3-1
P-value was calculated using chi-square test for categorical data.

As seen from table above, contrary to the sponsor's finding for evaluable patient analysis, the treatment difference failed to reach statistical significance for inadequate pain relief for treated patient population.

3.1.2.3.1.1 Subgroup Analysis

The results of subgroup analysis for inadequate pain relief are given below.

Inadequate Pain Relief by Subgroup
(Treated Patients)
Study C-2000-008

Subgroup	E-TRANS (fentanyl)	Placebo	Diff	p-value
Center				
3	8/18 (44.4%)	4/6 (66.7%)	-22.2%	0.6404
4	8/18 (44.4%)	3/6 (50.0%)	-5.5%	1.0000
5	6/18 (33.3%)	1/6 (16.7%)	16.7%	0.6287
6	2/10 (20.0%)	1/3 (33.3%)	-13.3%	1.0000
8	1/9 (11.1%)	3/3 (100%)	-88.9%	0.0182
10	5/18 (27.8%)	2/6 (33.3%)	-5.6%	1.0000
11	5/9 (55.6%)	1/3 (33.3%)	22.2%	1.0000
12	5/18 (27.8%)	3/6 (50.0%)	-22.2%	0.3618
13	7/18 (38.9%)	2/6 (33.3%)	5.6%	1.0000
14	1/18 (5.6%)	3/6 (50.0%)	-44.4%	0.0353
Gender				
Male	14/46 (30.4%)	6/16 (37.5%)	-7.1%	0.7572
Female	34/108 (31.5%)	17/35 (48.6%)	-17.1%	0.0720
Age				
<65	44/120 (36.7%)	17/40 (42.5%)	-5.8%	0.5742
≥65	4/34 (11.8%)	6/11 (54.5%)	-42.8%	0.0074
Surgery Type				
L. Abdominal	25/80 (31.3%)	11/26 (42.3%)	-11.1%	0.3010
Orth Bone	16/54 (29.6%)	8/20 (40.0%)	-10.4%	0.3974
Thoracic	0/2 (0.0%)			
U. Abdominal	7/17 (41.2%)	4/5 (80.0%)	-38.8%	0.1269
U. Abdominal L. Abdominal	0/1 (0.0%)			

P-value was obtained by Fisher's exact test.
Compiled by this reviewer.

As seen from the table above, the treatment difference in favor of E-TRANS (fentanyl) was inconsistent across center, gender, and age (<65 vs. ≥65).

3.1.2.3.2 Reviewer's Comments on Sponsor's Analysis of Secondary Endpoint

3.1.2.3.2.1 Dropout for Any Reason

The sponsor also performed analysis of dropout for any reason for treated patient population.

The number of patients withdrew from the study prematurely for any reason is given below.

Dropout for Any Reason
(Treated Patients)
Study C-2000-008

Treatment	For Any Reason	Diff (Fentanyl-Placebo)	P-value
E-TRANS(fentanyl)	58/154 (37.7%)	-19.2%	0.0162
Placebo	29/51 (56.9%)		

Copied from Table 11.3.3-1
P-value was calculated using chi-square test for categorical data.

As seen from the table above, the results from treated patient analysis were similar to those from sponsor's evaluable patient analysis.

3.1.2.3.2.2 Mean Pain Intensity

Contrary to the sponsor's finding based on last observation VAS, it was found that there was not treatment difference for patient intensity VAS scores after 24 hours for evaluable patients (p=0.849).

Furthermore, this reviewer performed additional analysis for pain intensity based on the change of last observation pain intensity from pain intensity at hour 0 for treated patients using the Wilcoxon test. The results are given below.

Change of Pain Intensity VAS Scores at Last Observation
(Treated Patients)
Study C-2000-008

	E-TRANS(fentanyl)	Placebo	p-value
N Mean VAS at hour 0 (SD)	151 42.75 (23.04)	51 44.37 (21.74)	0.8256
N Mean VAS at Last Observation (SD)	154 33.71 (29.55)	51 42.98 (31.47)	0.0463
N Mean Change of Last Observation from hour 0 (SD)	151 -8.95 (32.51)	51 -1.39 (37.57)	0.3199

As seen from the table above, contrary to the results from last observation, there was no treatment difference in the change of last observation pain intensity from pain intensity at hour 0 for treated patient population. So, the results from last observation might not be robust.

3.1.2.3.2.3 Patient Global Assessment

The sponsor also performed analysis of patient global assessment for treated patient population.

The results of patient global assessment are summarized below.

Patient Global Assessment
(Treated Patients)
Study C-2000-008

Assessment	(fentanyl) 40 µg	Placebo	p-value
Excellent	70 (45.5%)	14 (27.5%)	0.1416
Good	26 (16.9%)	11 (21.6%)	
Fair	19 (12.3%)	10 (19.6%)	
Poor	38 (24.7%)	16 (31.4%)	
Missing	1 (0.6%)	0 (0%)	

Copied from Table 11.3.3-7
P-value was calculated using chi-square test for categorical data.

As seen from the table above, the results from treated patient analysis were similar to those from sponsor's evaluable patient analysis.

3.1.2.3.2.4 Investigator Global Assessment

The sponsor also performed analysis of investigator global assessment for treated patient population.

The results of investigator global assessment are summarized below.

Investigator Global Assessment
(Treated Patients)
Study C-2000-008

Assessment	(fentanyl) 40 µg	Placebo	p-value
Excellent	76 (49.4%)	16 (31.4%)	0.1176
Good	26 (16.9%)	9 (17.6%)	
Fair	24 (15.6%)	11 (21.6%)	
Poor	27 (17.5%)	15 (29.4%)	
Missing	1 (0.6%)	0 (0%)	

Copied from Table 11.3.3-9
P-value was calculated using chi-square test for categorical data.

As seen from table above, contrary to the finding for the sponsor's evaluable patient analysis, the treatment difference failed to reach statistical significance for investigator global assessment for treated patient population.

3.1.2.3.2.5 Proportion of Patients Requiring Rescue Medication

The sponsor also performed analysis of proportion of patients requiring rescue medication for treated patient population.

The number of patients requiring rescue medication is given below.

Patients Requiring Rescue Medication
(Treated Patients)
Study C-2000-008

Treatment	Requiring Rescue Medication	Diff (Fentanyl-Placebo)	P-value
Fentanyl	79/154 (51.3%)	-7.5%	0.3506
Placebo	30/51 (58.8%)		

Copied from Table 11.2.4-8.
P-value was calculated using chi-square test for categorical data.

As seen from the table above, the results from treated patient analysis were similar to those from sponsor's evaluable patient analysis.

3.1.2.3.3 Analysis Requested by Medical Officer

The medical officer, Elizabeth McNeil, M.D., found that six patients (Patient No.: 321, 607, 1020, 1416, 1301, and 327) received prohibited analgesics during the study.

Per medical officer's request, this reviewer performed additional analysis for primary efficacy endpoint and some of secondary efficacy endpoints excluding these six patients (4 in E-TRANS and 2 in placebo). The p-value for inadequate pain relief changed to 0.1007 from 0.0700 [48/150 (32.0%) vs. 22/49 (44.9%)]. The p-values changed to

0.2119 and 0.1624 from 0.1416 and 0.1176 for patient global assessment and investigator global assessment, respectively. So, the sponsor's finding from this study might not be robust.

3.1.3 Study C-95-016

3.1.3.1 Study Design

This is a single-center, randomized, double-blind, placebo-controlled, parallel-group trial to evaluate the safety and efficacy of E-TRANS (fentanyl HCl) for the treatment of postoperative pain.

The primary objective of this trial was to compare the safety and efficacy of the E-TRAN (fentanyl HCl) system versus the E-TRANS (placebo) system in the management of the first 24 hours of postoperative pain.

After recovery from general or regional anesthesia, patients were titrated to an acceptable level of comfort using iv doses of morphine, fentanyl, sufentanil, or alfentanil. If they met the entry criteria, patients were randomized in a 3:1 ratio to E-TRANS (fentanyl): E-TRANS (placebo). Analgesia was then supplied by E-TRANS (fentanyl) or E-TRANS (placebo) for up to 24 hours.

All patients continued to participate in the study for either 24 hours or until one of following occurred, whichever occurred first:

- 80 on-demand doses had been delivered from the E-TRANS system applied to the patient;
- the patient's pain control was judged to be inadequate;
- the E-TRANS system was suspected of having a technical failure;
- any of the reasons for withdrawal.

The primary efficacy measurement was the number of patients in each treatment group who dropped out of the study due to insufficient efficacy (i.e., patients whose pain control was judged by the investigator's staff to be inadequate more than three hours after E-TRANS (fentanyl) or E-TRANS (placebo) treatment had been initiated and who therefore required termination from the study).

Secondary efficacy measurement included:

Pain Intensity: Pain intensity was measured on a 100-mm ungraded visual analog scale (VAS) that ranges from "no pain" (0) to "worst possible pain" (100). The pain assessment was made immediately before titration with iv opioids; immediately before the E-TRANS (fentanyl) or E-TRANS (placebo) treatment was initiated; at 0.5, 1-, 2-, 3-, 4-, 6-, 8-hour, and every 4 hours thereafter through the remainder of the study.

Patient Global Assessment: The patient global assessment was obtained at the time the E-TRANS treatment was terminated. The assessment consisted of a categorical

evaluation (poor, fair, good and excellent) of the E-TRANS method pain control. If the patient was withdrawn from the study prior to the 24-hour time point, the patient global assessment was completed at the time of withdrawal.

Investigator Global Assessment: Investigator global assessments of the method of pain control (poor, fair, good and excellent) was obtained at the time the E-TRANS treatment was terminated. If the patient was withdrawn from the study prior to the 24-hour time point, the investigator global assessment was completed at the time of withdrawal.

Primary efficacy parameter was withdrawal from the trial ≥3 hours after system application because of inadequate pain control. Other efficacy parameters were withdrawal from the trial for any reason, patient assessment of pain intensity (using a VAS of 0 to 100), and patient and investigator global assessments.

Patients who were withdrawn within the first three hours after initiation of E-TRANS treatment were replaced until 72 evaluable patients were enrolled in the E-TRANS (fentanyl) treatment group and 24 evaluable patients in the E-TRANS (placebo) treatment group.

The primary efficacy parameter was the dropout rate due to insufficient efficacy during the 24-hour treatment period. Insufficient efficacy was defined as a patient whose pain control was judged by the investigator's staff to be inadequate more than three hours after initiation of the treatment period (Hour 0) and who therefore required termination from the study.

Additional efficacy parameters were:

(1) Overall dropout rate regardless of termination reason during the 24-hour treatment period.
(2) Mean pain intensity over the 24-hour E-TRANS treatment period.
(3) The patient global assessment at the time of treatment termination.
(4) The investigator global assessment at the time of treatment termination.
(5) Proportion of patients requiring retitration to comfort within the first three hours after treatment initiation.

A total of 102 patients in New Zealand were enrolled into this study. Seventy seven (77) patients were randomized to receive E-TRANS (fentanyl); 25 patients were randomized to receive E-TRANS (placebo).

Of the 102 treated patients, 21 patients [9 E-TRANS (fentanyl), 12 E-TRANS (placebo)] discontinued the study early. A total of 81 patients [68 E-TRANS (fentanyl), 13 E-TRANS (placebo)] were considered study completers having either completed the 24-hour treatment period or having used the 80-doses available before 24 hours. A total of 99 patients [77 E-TRANS (fentanyl), 22 E-TRANS (placebo)] received at least 3 hours of treatment and were considered evaluable.

3.1.3.2 Sponsor's Analysis

3.1.3.2.1 Planned Analysis

Two sample test based on the proportion was used for the analysis of the primary efficacy parameter.

An event rate, dropout rate due to insufficient efficacy, of 70% for the E-TRANS (placebo) control group during the 24-hour E-TRANS treatment period was assumed. The sample size of 96 patients, with three-to-one enrollment ratio (72 patients in the E-TRANS (fentanyl) treatment group and 24 patients in the E-TRANS (placebo) treatment group) provided 90% power to detect a 40% event rate difference during the 24-hour treatment period between the E-TRANS (fentanyl) treatment group and the E-TRANS (placebo) control group at a significance level of α=0.05. To allow for a 10% dropout rate prior to the patients becoming evaluable, an enrollment of up 108 patients for this study was planned.

A two sample test based on the proportion was used for the analysis of the secondary efficacy parameters (1) overall dropout rate regardless of termination reason during the 24-hour treatment period, and (5) proportion of patients requiring retitration to comfort within the first three hours after treatment initiation.

A two sample t-test was used for analysis of the numerical secondary efficacy parameters.

A two sample test based on the proportion was employed for the analysis of the dichotomous patient and investigator global assessment data (good/excellent and otherwise). In addition, the Cochran-Mantel-Haenszel (CMH) method with integer score for the test of mean scores difference was used for the analysis of the four-point categorical scale patient and investigator global assessment data.

3.1.3.2.2 Treatment Group Comparability

Appendix Table 3 presents the demographic and baseline characteristics of all treated patients.

As seen from Appendix Table 3, the two treatment groups were similar with respect to demographic characteristics, surgery type and post-operative ASA physical status.

3.1.3.2.3 Sponsor's Analysis of Primary Efficacy Variable

The primary efficacy parameter was the dropout rate due to insufficient efficacy during the 24-hour treatment period.

The number of patients withdrew from the study prematurely because of inadequate pain control after the first 3 hours on study are given below.

Inadequate Pain Relief
(Evaluable Patients)
Study C-95-016

Treatment	Inadequate Pain Relief	Diff (Fentanyl-Placebo)	P-value
Fentanyl	6/77 (7.8%)	-33.1%	0.0001
Placebo	9/22 (40.9%)		

Copied from Table 11.2.3-1
P-value was calculated using chi-square test for categorical data.

As seen from table above, the proportion of dropouts for inadequate pain relief was statistically significantly less for the active than the placebo treatment group.

3.1.3.2.4 Sponsor's Analysis of Secondary Efficacy Variables

Mean pain intensity over the 24-hour time period was not computed for each patient due to number of missing measurements. About 6% of the observations were missing across the two treatment groups combined (52/817 for E-TRANS (fentanyl) and 14/205 for E-TRANS (placebo)). Instead, a patient's last pain measurement was used to assess the difference in pain intensity between the two treatment groups.

If general, if a patient had a missing PGA/IGA the assessment was considered "Poor" or "Failure" for the purpose of analysis. As an exception to this rule there were 3 placebo patients who did not have any patient or investigator global assessments. These three patients terminated the study due to suspected technical failure of the system and hence were not included in the PGA/IGA analysis as failure.

3.1.3.2.4.1 Overall Dropout Rate

The number of patients withdrew from the study prematurely for any reason is given below.

Dropout for Any Reason
(Evaluable Patients)
Study C-95-016

Treatment	For Any Reason	Diff (Fentanyl-Placebo)	P-value
Fentanyl	9/77 (11.7%)	-29.2%	0.0017
Placebo	9/22 (40.9%)		

Copied from Table 11.2.3-1
P-value was calculated using chi-square test for categorical data.

As seen from the table above, the proportion of dropouts for any reason was statistically significantly less for the active than the placebo treatment group.

3.1.3.2.4.2 Mean Pain Intensity

Mean values for pain intensity calculated by time point and by treatment group are summarized below.

Pain Intensity VAS Scores by Time
(Evaluable Patients)

	Treatment Group					
	E-TRANS (fentanyl) 40 µg (n=77)			Placebo (n=22)		
	No. of Patients	No. of Patients with VAS Scores	Mean VAS (SEM)	No. of Patients	No. of Patients with VAS Scores	Mean VAS (SEM)
Hours post-enrollment						
0	77	77	31.6 (1.51)	22	22	36.5 (2.85)
0.5	77	77	35.9 (1.95)	22	22	39.5 (3.69)
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 (0.0006)[a]	77	77	20.6 (1.93)	22	22	37.3 (5.76)

Note: Only patients with a pain intensity score at the given time point are included in the calculation of the mean.
[a] p-value for the difference between the averages of the last pain assessment for the two treatments was based on an ANOVA.

Scores for the last observation VAS were significantly lower for the active than for placebo treatment.

3.1.3.2.4.3 Patient Global Assessment

The results of patient global assessment are summarized below.

Patient Global Assessment
(Evaluable Patients)
Study C-95-016

Assessment	(fentanyl) 40 µg	Placebo	p-value
Excellent	49 (63.6%)	4 (18.2%)	0.0006
Good	20 (26.0%)	9 (40.9%)	
Fair	4 (5.2%)	5 (22.7%)	
Poor	4 (5.2%)	4 (18.2%)	

Copied from Table 11.2.3-7
P-value was calculated using chi-square test for categorical data.

As seen from the table above, there was significant treatment difference in favor of E-TRANS (fentanyl) in terms of patient global assessment.

3.1.3.2.4.4 Investigator Global Assessment

The results of investigator global assessment are summarized below.

Investigator Global Assessment
(Evaluable Patients)
Study C-95-016

Assessment	(fentanyl) 40 µg	Placebo	p-value
Excellent	47 (61.0%)	4 (18.2%)	0.0003
Good	22 (28.6%)	9 (40.9%)	
Fair	6 (7.8%)	4 (18.2%)	
Poor	2 (2.6%)	5 (22.7%)	

Copied from Table 11.2.3-9
P-value was calculated using chi-square test for categorical data.

As seen from the table above, there was significant treatment difference in favor of E-TRANS (fentanyl) in terms of investigator global assessment.

3.1.3.2.4.5 Proportion of Patients Requiring Rescue Medication

The number of patients requiring rescue medication is given below.

Patients Requiring Rescue Medication
(Evaluable Patients)
Study C-95-016

Treatment	Requiring Rescue	Diff (Fentanyl-Placebo)	P-value
E-TRANS(fentanyl)	26/77 (33.8%)	-2.6%	0.8210
Placebo	8/22 (36.4%)		

Copied from Table 5.4.7
P-value was calculated using chi-square test for categorical data.

As seen from the table above, there was no treatment difference in terms of proportion of patients requiring rescue medication.

3.1.3.3 Reviewer's Comments and Evaluation

There were three placebo patients were excluded from sponsor's evaluable patients analysis.

3.1.3.3.1 Reviewer's Comments on Sponsor's Analysis of Primary Efficacy Endpoint

The sponsor also performed analysis of primary efficacy endpoint for all treated patients.

The number of patients withdrew from the study prematurely because of inadequate pain control after the first 3 hours on study are given below.

Inadequate Pain Relief
(All Treated Patients)
Study C-95-016

Treatment	Inadequate Pain Relief	Diff (Fentanyl-Placebo)	P-value
E-TRANS(fentanyl)	6/77 (7.8%)	-28.2%	0.0005
Placebo	9/25 (36.0%)		

Copied from Table 11.2.3-1
P-value was calculated using chi-square test for categorical data.

As seen from table above, the proportion of dropouts for inadequate pain relief was statistically significantly less for the active than the placebo treatment group.

3.1.3.3.1.1 Subgroup Analysis

The results of subgroup Analysis for inadequate pain relief are given below.

Inadequate Pain Relief by Subgroup
(Treated Patients)
Study C-95-016

Subgroup	E-TRANS (fentanyl)	Placebo	Diff	p-value.
Gender				
Male	2/14 (14.3%)	0/3 (0.0%)	14.3%	1.0000
Female	4/63 (6.4%)	9/22 (40.9%)	-34.6%	0.0004
Age				
<65	6/71 (8.5%)	8/23 (34.8%)	-26.3%	0.0047
≥65	0/6 (0.0%)	1/2 (50.0%)	-50.0%	0.2500
Surgery Type				
L. Abdominal	4/58 (6.9%)	7/18 (38.9%)	-32.0%	0.0026
Orth Bone	2/16 (12.5%)	2/6 (33.3%)	-20.8%	0.2919
U. Abdominal	0/3 (0.0%)			
Other		0/1 (0%)		

P-value was obtained by Fisher's exact test.
Compiled by this reviewer.

As seen from table above, due to inadequate sample size for placebo, the results for males, patients aged ≥65 and patients with surgery type of orthopedic bone were not reliable and can not be interpreted.

3.1.3.3.2 Reviewer's Comments on Sponsor's Analysis of Secondary Efficacy Endpoint

The sponsor also performed analysis of secondary efficacy endpoints for all treated patients. The sponsor stated in the report that while mean values and frequency distribution changed slightly in the efficacy analysis of all treated patients, the overall

results of statistically significance finding between the two treatment group were the same as the analyses for evaluable patients.

Three patients in the placebo group had system technical failure and did not administer any on-demand dose. Hence there were no patient and investigator global assessments. In analysis of patient and investigator global assessment, the sponsor considered these patients as missing were not included in the analyses.

For best case scenario, if the outcomes for these 3 placebo patients were assumed as "excellent", the resulting p-values would be 0.0058 and 0.0031 for patient global assessment and investigator global assessment, respectively.

3.1.3.3.2.1 Overall Dropout Rate

Per medical officer's request, this reviewer performed analysis of over dropout rate for treated patients. The number of patients withdrew from the study prematurely for any reason is given below.

Dropout for Any Reason
(Treated Patients)
Study C-95-016

Treatment	For Any Reason	Diff (Fentanyl-Placebo)	P-value
E-TRANS (fentanyl)	9/77 (11.7%)	-36.3%	<0.0001
Placebo	12/25 (48.0%)		

Compiled by this reviewer.
P-value was calculated using chi-square test for categorical data.

As seen from the table above, the results from treated patient analysis were similar to those from sponsor's evaluable patient analysis.

3.1.4 Study C-2000-007

3.1.4.1 Study Design

This is a multicenter (33 sites), open-label, randomized, active-controlled, parallel-group study designed to evaluate the safety and efficacy of E-TRANS (fentanyl) treatments compared to IV PCA morphine treatment for the management of acute moderate to severe post-operative pain requiring opioid analgesia for up to 3 consecutive days (72 hours).

The objective of this study was to compare the safety and efficacy of E-TRANS (fentanyl) treatment with IV PCA morphine treatment for the management of post-operative pain.

Within each of the two strata defined by surgery type, the patient was randomized equally into one of two treatment groups: E-TRANS (fentanyl) or IV PCA morphine.

After recovery from general or regional anesthesia, some patients might require titration to an acceptable level of comfort using iv doses of morphine, fentanyl, sufentanil, or alfentanil. If they met the entry criteria, patients were randomized in a 1:1 ratio to E-TRANS (fentanyl): IV PC morphine. If the patient continued to require parenteral opioid after 24 hours, the patient might continue to use E-TRANS (fentanyl) or IV PCA morphine for up to two additional 24-hour treatment periods.

The E-TRANS (fentanyl) system was removed at the end of each 24-hour treatment period and a new system was replaced at a different location on patient's chest or upper arm.

At each 24-hour assessment point, the patient and the investigator completed global assessments. If the patient was withdrawn from the study prior to any 24-hour time point, the pain intensity measurement and global assessments were completed at the time of withdrawal.

The primary efficacy measurement was the patient global assessment collected at the 24-hour time point. If the patient was withdrawn from the study prior to the 24-hour time point, the patient global assessment was completed at the time of withdrawal. The assessment consisted of a categorical evaluation (poor, fair, good and excellent) of the method of pain control.

Secondary efficacy measurement included:

Patient Global Assessments: Patient global assessments was collected at the 48- and 72 hour time points for patients who remained in the study.

Pain Intensity: Pain intensity was measured on a 100-mm ungraded visual analog scale (VAS) that ranges from "no pain" (0) to "worst possible pain" (100). The pain assessment was made immediately before the E-TRANS (fentanyl) or IV PCA morphine treatment was initiated (Hour 0); at 0.5-, 1-, 2-, 3-, 4-, 6-, 8-hour, and every 4 hours thereafter through the remainder of the study.

Investigator Global Assessment: Investigator global assessments of the method of pain control (poor, fair, good and excellent) was obtained at the 24-hour time point and at the 48- and 72- hour time points for patients who remained in the study. If the patient was withdrawn from the study prior to the 24-hour time point, the investigator global assessment was completed at the time of withdrawal.

Number of Patients with Inadequate Pain Control: The number of patients in the E-TRANS (fentanyl) and the IV PCA morphine treatment groups whose pain control was judged by the investigator's staff to be inadequate more than 3 hours after Hour 0 and who were therefore withdrawn from the study was tabulated.

The primary efficacy parameter was the success rate after 24-hour treatment period based on the patient global assessment data. The success rate was the proportion of

patients with a successful treatment outcome, which was defined as a response on the patient global assessment of "good" or "excellent."

Additional efficacy parameters were:

(1) Proportion of patients who were withdrawn from the study more than 3 hours after hour 0 due to a clinical judgment made by the investigator's staff that the patient's pain control was inadequate.
(2) Mean pain intensity over the 24-, 48-, and 72-hour treatment periods.
(3) Patient global assessment at the 24-, 48- and 72-hour assessments.
(4) Investigator global assessment at the 24-, 48- and 72-hour assessments.

Of the 726 patients screened, 636 were randomized to E-TRANS (fentanyl) or IV PCA morphine pump applied (316 E-TRANS (fentanyl), 320 IV PCA morphine).

A total of 626 patients (310 E-TRANS (fentanyl), 316 IV PCA morphine) who received at least 3 hours of treatment and completed a patient global assessment were considered evaluable.

3.1.4.2 Sponsor's Analysis

3.1.4.2.1 Planned Analysis

For the analysis of primary efficacy parameter, the two-sided 95% confidence interval of the difference in the success rate between the two treatments was constructed in the final analyses. E-TRANS (fentanyl) was considered therapeutically equivalent to IV PCA morphine if the lower boundary of the confidence interval is greater than or equal to -10%.

All data from all centers and surgery types were pooled.

A 95% confidence interval of the difference in the proportion of patients for the two treatments who were withdrawn from the study more than 3 hours after Hour 0 due to clinical judgment made by the investigator's staff that the patient's pain control was inadequate was constructed.

The pain intensity was analyzed in two parts. An analysis was conducted for the first 3 hours after Hour 0 when the study medications might be augmented with rescue medication to provide pain relief. A second analysis was conducted for the remaining hours of the first 24-hour treatment period. A two-way analysis of variance (ANOVA) model was used for the analysis of the mean pain intensity. The ANOVA model included treatment, surgery type, and treatment-surgery type as factors. The interaction factor was not retained in the final model unless they were significant at significance level of 0.10. A similar two-way ANOVA model approach was used for analysis of the mean pain intensity scores for the second and third 24-hour treatment periods.

The primary efficacy analysis was the construction of a 95% confidence interval for the difference in the success rate based on the patient global assessment data between two treatment groups, E-TRANS (fentanyl) and IV PCA morphine.

All statistical tests for the efficacy analyses were performed at α=0.05 significance level. The statistical tests used for the analysis of baseline data were at a level of significance of 0.10. All tests were two-tailed.

A sample size of 504 evaluable patients (252 patients in each treatment group) was planned for this study. The sample size provided 80% power to demonstrate the therapeutic equivalence in proportion between two treatments.

Two treatments was considered therapeutically equivalent if the 95% confidence interval of the difference in success rate falls within ±10% based on two one-sided tests with α=0.025 and a maximum acceptance difference of 10%.

Assuming a success rate of 80% for both E-TRANS (fentanyl) and the IV PCA morphine treatment groups, a sample size of 252 patients was needed for each treatment group (Makuch and Simon, 1978).

To allow for a 20% dropout rate prior to the patient becoming evaluable, an enrollment of up to 630 patients for this was planned.

3.1.4.2.2 Treatment Group Comparability

Attached Table 4 presents the demographic and baseline characteristics of all treated patients.

As seen from Attached Table 4, the two treatment groups were similar with respect to demographic characteristics, surgery type and post-operative ASA physical status.

3.1.4.2.3 Sponsor's Analysis of Primary Efficacy Variable

The primary efficacy parameter was the first 24-hour patient global assessment. The results of analysis of patient global assessment after the first 24-hours of treatment for evaluable patients and treated patients populations are given below.

Patient Global Assessment after the First 24 Hours of Treatment

	E-TRANS® (fentanyl) 40 µg	IV PCA Morphine	p-value
Evaluable Patients			
n	310	316	0.3756
Success	232 (74.8%)	246 (77.8%)	
Failure	75 (24.2%)	64 (20.3%)	
Missing	3 (1.0%)	6 (1.9%)	
Difference in Success Rate Between Two Treatments	-3%		
95% CI for the Difference in Success Rate	(-9.7%, 3.7%)		
Treated Patients			
n	316	320	0.3584
Success	233 (73.7%)	246 (76.9%)	
Failure	80 (25.3%)	68 (21.3%)	
Missing	3 (0.9%)	6 (1.9%)	
Difference in Success Rate Between Two Treatments	-3.2%		
95% CI for the Difference in Success Rate	(-9.9%, 3.5%)		

Success = Good or Excellent
Failure = Poor or Fair
Source: Tables 11.2.3.1-2 and 11.3.3.1-2

3.1.4.2.4 Sponsor's Analysis of Secondary Efficacy Variables

3.1.4.2.4.1. 48-Hour, 72-Hour, and Last Patient Global Assessment

The results of analysis 48-hour, 72-hour, and last patient global assessment are given below.

48-Hour, 72-Hour, and Last Patient Global Assessments

	E-TRANS® (fentanyl) 40 µg	IV PCA Morphine	p-value
48 Hour Assessment for Evaluable Patients			
n	183	191	
Success	158 (86.3%)	159 (83.2%)	
72 Hour Assessment for Evaluable Patients			
n	77	69	
Success	70 (90.9%)	56 (81.2%)	
Last Assessment for Evaluable Patients			
n	310	316	
Success	234 (75.5%)	250 (79.1%)	0.2782
Last Assessment for Treated Patients			
n	316	320	
Success	235 (74.4%)	250 (78.1%)	0.2654

Source: Tables 11.2.3.1-5, 11.2.3.1-8, and 11.3.3.1-5

40-Hour, 72-Hour, and Last Patient Global Assessment 95% Confidence Interval

	Difference (Etran- PCA)	95% C.I.
48 Hour for Evaluable Patients	3.1%	(-4.2%, 10.4%)
72 Hours for Evaluable Patients	9.7%	(-1.5%, 21.0%)
Last Assessment for Evaluable Patients	-3.6%	(-10.2%, 2.9%)
Last Assessment for Treated Patients	-3.8%	(-10.4%, 2.9%)

Compiled by this review.

3.1.4.2.4.2 24-Hour Investigator Global Assessment

The results of analysis of investigator global assessment after first 24 hours of treatment are given below.

Investigator Global Assessment after First 24 Hours of Treatment

	E-TRANS® (fentanyl) 40 µg	IV PCA Morphine	p-value
Evaluable Patients			
n	310	316	0.4644
Success	249 (80.3%)	261 (82.6%)	
Failure	57 (18.4%)	48 (15.2%)	
Missing	4 (1.3%)	7 (2.2%)	
Difference in Success Rate Between Two Treatments	-2.3%		
95% CI for the Difference in Success Rate	(-8.4%, 3.8%)		
Treated Patients			
n	316	320	0.3817
Success	249 (78.8%)	261 (81.6%)	
Failure	63 (19.9%)	52 (16.3%)	
Missing	4 (1.3%)	7 (2.2%)	
Difference in Success Rate Between Two Treatments	-2.8%		
95% CI for the Difference in Success Rate	(-9.0%, 3.4%)		

Source: Tables 11.2.3.2-2 and 11.3.3.2-2

3.1.4.2.4.3 48-Hour, 72-Hour, and Last Investigator Global Assessments

The results of analysis 48-hour, 72-hour, and last patient global assessment are given below.

48-Hour, 72-Hour, and Last Investigator Global Assessments

	E-TRANS® (fentanyl) 40 µg	IV PCA Morphine	p-value
48 Hour Assessment for Evaluable Patients			
n	184	193	
Success	165 (89.7%)	170 (88.1%)	
72 Hour Assessment for Evaluable Patients			
n	78	69	
Success	71 (91.0%)	56 (81.2%)	
Last Assessment for Evaluable Patients			
n	310	316	
Success	249 (80.3%)	262 (82.9%)	0.4030
Last Assessment for Treated Patients			
n	316	320	
Success	249 (78.8%)	262 (81.9 %)	0.3288

Source: Tables 11.2.3.2-5, 11.2.3.2-8, and 11.3.3.2-5

40-Hour, 72-Hour, and Last Patient Global Assessment
95% Confidence Interval

	Difference (Etran- PCA)	95% C.I.
48 Hour for Evaluable Patients	1.6%	(-4.8%, 9.9%)
72 Hours for Evaluable Patients	9.9%	(-1.3%, 21.1%)
Last Assessment for Evaluable Patients	-2.6%	(-8.7%, 3.5%)
Last Assessment for Treated Patients	-3.1%	(-9.3%, 3.1%)

Compiled by this review.

3.1.4.2.4.4 Mean Pain Intensity

Mean VAS after first 24 hour and mean VAS at last observation for pain intensity calculated by treatment group are summarized below

Pain Intensity VAS Scores After 24 Hours and at Last Observation

	E-TRANS® (fentanyl) 40 µg	IV PCA Morphine	p-value
Evaluable Patients			
n	310	316	
Mean VAS after first 24h (SEM)	31.9 (1.57)	30.6 (1.43)	0.5179
Mean VAS at Last Observation (SEM)	27.1 (1.61)	27.6 (1.47)	0.8430
Treated Patients			
n	316	320	
Mean VAS after first 24h (SEM)	32.7 (1.58)	31.1 (1.45)	0.4548
Mean VAS at Last Observation (SEM)	28.0 (1.62)	28.2 (1.49)	0.9458

Source: Tables 11.2.3.4-1 and 11.3.3.4-1

3.1.4.2.4.5 Proportion of Patients Requiring Rescue Medication

The number of patients requiring rescue medication in the first 3 hours after enrollment to retitrate patients to comfort is given below.

Patients Requiring Rescue Medication

	E-TRANS® (fentanyl) 40 µg	IV PCA Morphine	p-value
Evaluable Patients			
n	310	316	
Did require rescue medication	66 (21.3%)	84 (26.6%)	0.1209
Treated Patients			
n	316	320	
Did require rescue medication	72 (22.8%)	87 (27.2%)	0.1998

Source: Tables 11.2.4-9 and 11.3.4-9

Patients Requiring Rescue Medication
95% Confidence Interval

	Difference (Etran- PCA)	95% C.I.
Evaluable Patients	-5.3%	(-12.0%, 1.4%)
Evaluable Patients	-4.4%	(-11.1%, 2.3%)

Compiled by this review.

As seen from the table above, the proportions of patients who required rescue medication were similar for both treatment groups for both evaluable patients and treated patients analyses.

3.1.4.3 Reviewer's Comments and Evaluation

3.1.4.3.1 Reviewer's Comments on the Equivalence Margin

The equivalence margin of 10% was arbitrary. There was no justification provided.

3.1.4.3.2 Inadequate Pain Relief

The sponsor failed to include the result from analysis of proportion of patients who were withdrawn from the study more than 3 hours after Hour 0 due to inadequate pain relief in the report. But, this endpoint was pre-specified in the sponsor's protocol as a secondary efficacy endpoint.

The number of patients withdrew from the study prematurely because of inadequate pain control after the first 3 hours on study are given below.

Inadequate Pain Relief
(Evaluable Patients)
Study C-2000-007

Treatment	Inadequate Pain Relief	Diff (Fentanyl- IV PCA)	95% C.I.
E-TRANS (Fentanyl)	44/310 (12.2%)	4.7%	(-0.4%, 9.8%)
IV PCA morphine	30/316 (9.5%)		

Copied from Table 11.2.3.3-1
P-value was calculated using chi-square test for categorical data.

Inadequate Pain Relief
(Treated Patients)
Study C-2000-007

Treatment	Inadequate Pain Relief	Diff (Fentanyl- IV PCA)	95% C.I.
E-TRANS (Fentanyl)	49/316 (15.5%)	4.9%	(-0.3%, 10.18%)
IV PCA morphine	34/320 (10.6%)		

Copied from Table 11.3.3.3.3-1.
P-value was calculated using chi-square test for categorical data.

As seen from the tables above, for inadequate pain relief, the treatment difference was about 5% in favor of IV PCA morphine. The 95% confidence interval of treatment difference was not symmetric [(-0.4%, 9.8%) for evaluable patients, (-0.3%, 10.18%) for treated patients] and indicated that the probability of that E-TRANS (fentanyl) was worsen than IV PCA morphine by 10% was 5%. The upper limit of 95% confidence interval of treatment difference might be too large to make conclusion that E-TRANS (fentanyl) treatment is therapeutically equivalent to an IV PCA morphine regimen.

3.1.4.3.2.1 .Subgroup Analysis

The results of subgroup analysis of inadequate pain relief are given below.

Inadequate Pain Relief by Subgroup
(Treated Patients)
Study C-2000-007

Subgroup	E-TRANS (fentanyl)	IV PCA	Diff	95% C.I.
Gender				
Male	19/87 (21.8%)	14/82 (17.1%)	4.8%	(-7.14%, 16.67%)
Female	30/229 (13.1%)	20/238 (8.4%)	4.7%	(-0.92%, 10.31%)
Age				
<65	37/242 (15.3%)	28/258 (10.9%)	4.4%	(-1.48%, 10.35%)
≥65	12/74 (16.2%)	6/62 (9.7%)	6.5%	(-4.63%, 17.71%)

Compiled by this reviewer.

As seen from the tables above, for inadequate pain relief, the treatment difference was about 5% to 7% in favor of IV PCA morphine across subgroups of gender and age. The 95% confidence interval of treatment differences were not symmetric.It was indicated that the probability of that E-TRANS (fentanyl) was worsen than IV PCA morphine by 17% for male patients was 5%. The probability of that E-TRANS (fentanyl) was worsen than IV PCA morphine by 18% for patients aged greater or equal to 65 was 5%. These upper limits of 95% confidence intervals of treatment difference might be too large to make conclusion that E-TRANS (fentanyl) treatment is therapeutically equivalent to an IV PCA morphine regimen.

3.1.4.3.3 Overall Dropout Rate

The number of patients withdrew from the study prematurely for any reason is given below.

Dropout for Any Reason
(Evaluable Patients)
Study C-2000-007

Treatment	For Any Reason	Diff (Fentanyl- IV PCA)	95% C. I.
E-TRANS (Fentanyl)	76/310 (24.5%)	0.5%	(-6.3%, 7.2%)
IV PCA morphine	76/316 (24.1%)		

Copied from Table 11.2.3-1.
P-value was calculated using chi-square test for categorical data.

Dropout for Any Reason
(Treated Patients)
Study C-2000-007

Treatment	For Any Reason	Diff (Fentanyl- IV PCA)	95% C. I.
E-TRANS (Fentanyl)	82/316 (25.9%)	0.9%	(-5.8%, 7.7%)
IV PCA morphine	8-/320 (25.0%)		

Copied from Table 11.3.3.3-1.
P-value was calculated using chi-square test for categorical data.

As seen from the table above, E-TRANS (fentanyl) treatment was similar to an IV PCA morphine regimen.

3.1.4.3.4 Reviewer's Comments on Sponsor's Analysis of Primary Endpoint

There were 3 E-TRANS (fentanyl) treated patients and 6 IV PCA morphine treated patients who did not have patient global assessment score. In the sponsor's analysis, these patients were considered to "failure." The results from the sponsor's analysis tend to narrow the confidence interval of the difference and tend to be biased in favor of test drug.

For more conservative, the best case scenario should be used. In the "best case scenario," all patients without patient global assessment score are considered as "success." This reviewer performed the "best case" analysis of primary endpoint. The results are given below.

Patient Global Assessment after the First 24 Hours of Treatment
(Evaluable Patients)
Study C-2000-007

Treatment	Success	Diff (Fentanyl- IV PCA)	95% C.I.
E-TRANS (Fentanyl)	235/310 (75.8%)	-3.9%	(-10.5%, 2.6%)
IV PCA morphine	252/316 (79.7%)		

Compiled by this reviewer.

Patient Global Assessment after the First 24 Hours of Treatment
(Treated Patients)
Study C-2000-007

Treatment	Success	Diff (Fentanyl-IV PCA)	95% C.I.
E-TRANS (Fentanyl)	236/316 (74.7%)	-4.1%	(-10.6%, 2.5%)
IV PCA morphine	252/320 (78.8%)		

Compiled by this reviewer.

As seen from tables above, contrary to sponsor's finding, the lower limit of 95% confidence interval of the treatment difference in success rate was just slight less than

-10%, the pre-specified equivalence marginal for both evaluable and treatment patient analysis. Furthermore, the lower limit of 95% confidence interval of treatment difference might be too large to make conclusion that E-TRANS (fentanyl) treatment is therapeutically equivalent to an IV PCA morphine regimen.

3.1.4.3.4.1 Subgroup Analysis

The results of subgroup analysis for patient global assessment after the first 24 hours of treatment are given below.

Patient Global Assessment after the First 24 Hours of Treatment by Subgroup (Treated Patients)
Study C-2000-007

Subgroup	E-TRANS (fentanyl)	IV PCA	Diff	95% C.I.
Gender				
Male	56/85 (65.9%)	61/81 (75.3%)	-9.4%	(-23.21%, 4.35%)
Female	177/228 (77.6%)	185/233 (79.4%)	-1.8%	(-9.27%, 5.73%)
Age				
<65	177/240 (73.8%)	202/254 (79.5%)	-5.8%	(-13.24%, 1.68%)
≥65	56/73 (76.7%)	44/60 (73.3%)	3.4%	(-11.43%, 18.18%)
Surgery Type				
L. Abdominal	153/181 (84.5%)	157/186 (84.4%)	0.1%	(-7.29%, 7.54%)
Orth Bone	66/114 (57.9%)	75/109 (68.8%)	-10.9%	(-23.48%, 1.65%)
Thoracic	4/4 (100.0%)	3/5 (60.0%)	40.0%	(-2.95%, 82.95%)
U. Abdominal	9/12 (75.0%)	10/13 (76.9%)	-1.9%	(-34.47%, 31.62%)
L. Abdominal/	1/2 (50.0%)	1/1 (100%)	-50%	(-119.3%, 19.31%)

Compiled by this reviewer.

As seen from the tables above, for patient's global assessment, the treatment differences were about 9% and 11% in favor of IV PCA morphine for male patients and patients with orthopedic bone surgery, respectively. The 95% confidence interval of treatment differences were not symmetric.It was indicated that the probability of that E-TRANS (fentanyl) was worsen than IV PCA morphine by 23% for male patients was 5%. The probability of that E-TRANS (fentanyl) was worsen than IV PCA morphine by 23% for patients with orthopedic bone surgery was 5%. These upper limits of 95% confidence intervals of treatment difference might be too large to make conclusion that E-TRANS (fentanyl) treatment is therapeutically equivalent to an IV PCA morphine regimen.

3.1.4.3.5 Reviewer's Comments on Sponsor's Analysis of Secondary Endpoint

There were 4 E-TRANS (fentanyl) treated patients and 7 IV PCA morphine treated patients who did not have investigator global assessment score. In the sponsor's analyses, these patients were considered to "failure." The results from the sponsor's analyses tend to narrow the confidence interval of the difference and tend to be biased in favor of test drug.

For more conservative, the best case scenario should be used. In the "best case scenario," all patients without investigator global assessment score are considered as "success." This reviewer performed the "best case" analysis of patient global assessment after first 24 hours of treatment. The results are given below.

Investigator Global Assessment after the First 24 Hours of Treatment (Evaluable Patients) Study C-2000-007

Treatment	Success	Diff (Fentanyl- IV PCA)	95% C.I.
E-TRANS (Fentanyl)	253/310 (81.6%)	-3.2%	(-9.05%, 2.66%)
IV PCA morphine	268/316 (84.8%)		

Compiled by this reviewer.

Investigator Global Assessment after the First 24 Hours of Treatment (Treated Patients) Study C-2000-007

Treatment	Success	Diff (Fentanyl-IV PCA)	95% C.I.
E-TRANS (Fentanyl)	253/316 (80.1%)	-3.7%	(-9.67%, 2.29%)
IV PCA morphine	268/320 (83.8%)		

Compiled by this reviewer.

As seen from tables above, the results were similar to those given by sponsor's finding. However, the lower limit of 95% confidence interval of the treatment difference in success rate was just slight smaller than 10%, the pre-specified equivalence margin for both evaluable and treatment patient analyses.

3.2 Evaluation of Safety

In Study C-2001-011, overall, of the 484 patient treated in this study, 226 (46.7%) experienced at least one adverse event: 129 (52.9%) patients in the E-TRANS (fentanyl) group (n=244), and 97 (40.4%) patients in the placebo group (n=240).

Nausea was reported by 29.5% of E-TRANS (fentanyl) patients compared to 16.3% of placebo patients.

In Study C-2000-008, overall, of the 205 patient treated in this study, 125 (61.0%) experienced at least one adverse event: 99 (64.3%) patients in the E-TRANS (fentanyl) group (n=154), and 26 (51.0%) patients in the placebo group (n=51).

Nausea was reported by 36.4% of E-TRANS (fentanyl) patients compared to 25.5% of placebo patients, and vomiting occurred in 8.4% of E-TRANS (fentanyl) patients compared to 2.0 of placebo patients. Pruritus was reported by 5.8% of E-TRANS (fentanyl) patients and none of the placebo patients.

In Study C-95-016, the most common systemic adverse event was nausea of mild to moderate severity in both treatment groups. Events more prevalent with E-TRANS fentanyl treatment were application site reaction - erythema (79.2% vs. 20%), vomiting (41.6% vs. 20.0%) and pruritus (15.6% vs. 0%)) was higher for active than placebo treatment.

In Study C-2000-007, overall, of the 636 patient treated in this study, 496 (78.0%) experienced at least one adverse event: 243 (76.9%) patients in the E-TRANS (fentanyl) group (n=316), and 253 (79.1%) patients in the placebo group (n=320).

The most common adverse events were nausea (46.5%), fever (20.6%), headache (11.9%), pruritus (10.4%), and vomiting (10.2%). Adverse events reported at a higher incidence in the E-TRANS (fentanyl) group than in the IV PCA morphine group were headache (14.9% vs. 9.1%), vomiting (11.1% vs. 9.4%), constipation (4.4% vs. 2.8%), hypertension (2.2% vs. 0.9%), application-site erythema (2.2% vs. 0%), and application-site itching (2.2% vs. 0%). Conversely, the following events were reported at a higher incidence in the IV PCA morphine group than in the E-TRANS(fentanyl) group: nausea (49.1% vs. 44.0%), pruritus (12.5% vs. 8.2%), abdominal pain (3.8% vs. 2.8%), peripheral edema (3.8% vs. 0.9%), and tachycardia (2.8% vs. 1.3%).

4. FINDINGS IN SPECIAL/SUBGROUP POPULATION

4.1 Gender, Race and Age

No conclusion on race can be drawn due to lack of representation of Black and other races.

The results of subgroup analysis of inadequate pain relief by gender and age (<65 vs. ≥65) for Studies C-2001-011, C-2000- 008, C-95-016, and C-2000-007 are given below.

Inadequate Pain Relief by Subgroup
(Treated Patients)
Study C-2001-011

Subgroup	E-TRANS (fentanyl)	Placebo	Difference	p-value	Breslow-Day p-value
Gender					0.0675
Male	21/74 (28.4%)	44/70 (62.9%)	-34.5%	<0.0001	
Female	49/170 (28.8%)	100/170 (58.8%)	-30.0%	<0.0001	
Age					0.6527
<65	49/172 (28.5%)	120/187 (64.2%)	-35.7%	<0.0001	
≥65	21/72 (29.2%)	24/53 (45.3%)	-16.1%	0.0893	

P-values were obtained using Fisher's exact test
Compiled by this reviewer.

Inadequate Pain Relief by Subgroup
(Treated Patients)
Study C-2000-008

Subgroup	E-TRANS (fentanyl)	Placebo	Diff	p-value
Gender				
Male	14/46 (30.4%)	6/16 (37.5%)	-7.1%	0.7572
Female	34/108 (31.5%)	17/35 (48.6%)	-17.1%	0.0720
Age				
<65	44/120 (36.7%)	17/40 (42.5%)	-5.8%	0.5742
≥65	4/34 (11.8%)	6/11 (54.5%)	-42.8%	0.0074

P-value was obtained by Fisher's exact test.
Compiled by this reviewer.

Inadequate Pain Relief by Subgroup
(Treated Patients)
Study C-95-016

Subgroup	E-TRANS (fentanyl)	Placebo	Diff	p-value.
Gender				
Male	2/14 (14.3%)	0/3 (0.0%)	14.3%	1.0000
Female	4/63 (6.4%)	9/22 (40.9%)	-34.6%	0.0004
Age				
<65	6/71 (8.5%)	8/23 (34.8%)	-26.3%	0.0047
≥65	0/6 (0.0%)	1/2 (50.0%)	-50.0%	0.2500

P-value was obtained by Fisher's exact test.
Compiled by this reviewer.

Inadequate Pain Relief by Subgroup
(Treated Patients)
Study C-2000-007

Subgroup	E-TRANS (fentanyl)	IV PCA	Diff	95% C.I.
Gender				
Male	19/87 (21.8%)	14/82 (17.1%)	4.8%	(-7.14%, 16.67%)
Female	30/229 (13.1%)	20/238 (8.4%)	4.7%	(-0.92%, 10.31%)
Age				
<65	37/242 (15.3%)	28/258 (10.9%)	4.4%	(-1.48%, 10.35%)
≥65	12/74 (16.2%)	6/62 (9.7%)	6.5%	(-4.63%, 17.71%)

Compiled by this reviewer.

As seen from tables above, Studies C-2001-011, C-2000-008 and C-95-016 suggested that there was no gender or age effect on inadequate pain relief for comparing E-TRANS (fentanyl) group vs. placebo group.

Study C-2000-007 revealed that E-TRANS (fentanyl) group was worse than IV PCA group by about 5% in terms of inadequate pain relief across gender and age.

4.2 Other Special/Subgroup Population

The results of subgroup analysis of inadequate pain relief by surgery type for Studies C-2001-011, C-2000-008 and C-95-016 are given below.

Inadequate Pain Relief by Subgroup
(Treated Patients)
Study C-2001-011

Subgroup	E-TRANS (fentanyl)	Placebo	Difference	p-value	Breslow-Day p-value
Surgery Type					0.3372
Lower Abdominal	28/121 (23.1%)	71/115 (61.7%)	-38.6%	<0.0001	
Orthopedic Bone	40/113 (35.4%)	69/110 (62.8%)	-27.3%	<0.0001	
Thoracic	0/6 (0.0%)	0/7 (0.0%)	0.0%		
U. Abdominal	1/1 (100%)	1			
L. Abdominal					

P-values were obtained using Fisher's exact test
Compiled by this reviewer.

Inadequate Pain Relief by Subgroup
(Treated Patients)
Study C-2000-008

Subgroup	E-TRANS (fentanyl)	Placebo	Diff	p-value
Surgery Type				
L. Abdominal	25/80 (31.3%)	11/26 (42.3%)	-11.1%	0.3010
Orth Bone	16/54 (29.6%)	8/20 (40.0%)	-10.4%	0.3974
Thoracic	0/2 (0.0%)			
U. Abdominal	7/17 (41.2%)	4/5 (80.0%)	-38.8%	0.1269
U. Abdominal	0/1 (0.0%)			
L. Abdominal				

P-value was obtained by Fisher's exact test.
Compiled by this reviewer.

Inadequate Pain Relief by Subgroup
(Treated Patients)
Study C-95-016

Subgroup	E-TRANS (fentanyl)	Placebo	Diff	p-value.
Surgery Type				
L. Abdominal	4/58 (6.9%)	7/18 (38.9%)	-32.0%	0.0026
Orth Bone	2/16 (12.5%)	2/6 (33.3%)	-20.8%	0.2919
U. Abdominal	0/3 (0.0%)			
Other		0/1 (0%)		

P-value was obtained by Fisher's exact test.
Compiled by this reviewer.

As seen from tables above, Studies C-2001-011, C-2000-008 and C-95-016 indicated that E-TRANS (fentanyl) group was numerically superior to placebo group across surgery type in terms of inadequate pain relief.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The sponsor has submitted three placebo-controlled studies (C-2001-011, C-2000-008, and C-95-016) and one active-controlled study (C-2000-007) for the claim.

Study C-2001-011 showed that for the primary efficacy endpoint, the proportion of dropouts for inadequate pain relief, E-TRANS (fentanyl) treated group was statistically significantly better than the placebo treatment group for both evaluable and treated patient populations. Furthermore, treatment difference in favor of E-TRANS (fentanyl) was consistent across center, gender, age (<65 vs. ≥ 65) and ASA. For the secondary efficacy endpoints, the E-TRANS (fentanyl) was superior to placebo for dropout for any reason, pain intensity, patient global assessment and investigator global assessment for both evaluable and treated patients populations. Treatment difference in terms of proportion of patients requiring rescue medication was observed for treated patient population but not for evaluable patient population.

In Study C-2000-08, for the primary efficacy endpoint, the proportion of dropouts for inadequate pain relief, E-TRANS (fentanyl) treated group was marginally statistically significantly better than the placebo treatment group for evaluable patient population, but the treatment difference failed to reach statistical significance for treated patient population. Furthermore, the sponsor's finding from this study might not be robust. The treatment difference in favor of E-TRANS (fentanyl) was not internal consistent across center, gender, and age (<65 vs. ≥ 65). For the secondary efficacy endpoints, the E-TRANS (fentanyl) was superior to placebo for dropout for any reason for both evaluable and treated patient populations. But for other secondary efficacy endpoints: pain intensity, patient global assessment, investigator global assessment and proportion of patients requiring rescue medication, no statistically significant difference between E-TRANS (fentanyl) and placebo was shown for both evaluable and treated patient populations.

Study C-95-016, dominated by females (83%), showed that for the primary efficacy endpoint, the proportion of dropouts for inadequate pain relief, E-TRANS (fentanyl) treated group was statistically significantly better than the placebo treatment group for both evaluable and treated patient populations. Furthermore, treatment difference in favor of E-TRANS (fentanyl) was consistent across gender, age (<65 vs. ≥ 65) and surgery type. For the secondary efficacy endpoints, the E-TRANS (fentanyl) was superior to placebo for dropout for any reason, pain intensity, patient global assessment and investigator global assessment for both evaluable and treated patients populations.

No Treatment difference in terms of proportion of patients requiring rescue medication was observed for both evaluable and treated patient populations.

Study C-2000-07 was an open-label, randomized, active-controlled, parallel group study comparing E-TRANS (fentanyl) and IV PVA morphine treatment.

The equivalence margin of 10% was arbitrary without justification.

This study showed that for the primary efficacy endpoint, the first 24-hour patient global assessment, the lower limit of the 95 confidence interval of treatment difference (fentanyl – IV PCA) was just slightly greater than -10%, the pre-specified equivalence margin from the sponsor's analysis. But from this reviewer's analysis which included 9 additional patients (3 E-TRANS (fentanyl) treated patients and 6 IV PCA morphine treated patients) who did not have patient global assessment score and these patients were considered as "success", the lower limit of 95% confidence interval of the treatment difference in success rate was just slightly less than -10%, the pre-specified equivalence marginal for both evaluable and treated patient populations.

Furthermore, the lower limit of 95% confidence interval of treatment difference might be too large to make conclusion that E-TRANS (fentanyl) treatment is therapeutically equivalent to an IV PCA morphine regimen.

5.2 Conclusion and Recommendations

Study C-2001-011 showed that for the primary efficacy endpoint, the proportion of dropouts for inadequate pain relief, E-TRANS (fentanyl) treated group was statistically significantly better than the placebo treatment group for both evaluable and treated patient populations. Furthermore, treatment difference in favor of E-TRANS (fentanyl) was consistent across center, gender, age (<65 vs. ≥65) and ASA. For the secondary efficacy endpoints, the E-TRANS (fentanyl) was superior to placebo for dropout for any reason, pain intensity, patient global assessment and investigator global assessment for both evaluable and treated patients populations. Treatment difference in terms of proportion of patients requiring rescue medication was observed for treated patient population but not for evaluable patient population.

In Study C-2000-08, for the primary efficacy endpoint, the proportion of dropouts for inadequate pain relief, E-TRANS (fentanyl) treated group was marginally statistically significantly better than the placebo treatment group for evaluable patient population, but the treatment difference failed to reach statistical significance for treated patient population. Furthermore, the sponsor's finding from this study might not be robust. The treatment difference in favor of E-TRANS (fentanyl) was not internal consistent across center, gender, and age (<65 vs. ≥65). For the secondary efficacy endpoints, the E-TRANS (fentanyl) was superior to placebo for dropout for any reason for both evaluable and treated patient populations. But for other secondary efficacy endpoints: pain intensity, patient global assessment, investigator global assessment and proportion of patients requiring rescue medication, no statistically significant difference between

E-TRANS (fentanyl) and placebo was shown for both evaluable and treated patient populations.

Study C-95-016, dominated by females (83%), showed that for the primary efficacy endpoint, the proportion of dropouts for inadequate pain relief, E-TRANS (fentanyl) treated group was statistically significantly better than the placebo treatment group for both evaluable and treated patient populations. Furthermore, treatment difference in favor of E-TRANS (fentanyl) was consistent across gender, age (<65 vs. ≥ 65) and surgery type. For the secondary efficacy endpoints, the E-TRANS (fentanyl) was superior to placebo for dropout for any reason, pain intensity, patient global assessment and investigator global assessment for both evaluable and treated patients populations. No Treatment difference in terms of proportion of patients requiring rescue medication was observed for both evaluable and treated patient populations.

Study C-2000-07 was an open-label, randomized, active-controlled, parallel group study comparing E-TRANS (fentanyl) and IV PVA morphine treatment.

The equivalence margin of 10% was arbitrary without justification.

This study showed that for the primary efficacy endpoint, the first 24-hour patient global assessment, the lower limit of the 95 confidence interval of treatment difference (fentanyl – IV PCA) was just slightly greater than -10%, pre-specified equivalence margin from the sponsor's analysis. But from this reviewer's analysis which included 9 additional patients (3 E-TRANS (fentanyl) treated patients and 6 IV PCA morphine treated patients) who did not have patient global assessment score and these patients were considered as "success", the lower limit of 95% confidence interval of the treatment difference in success rate was just slightly less than -10%, pre-specified equivalence marginal for both evaluable and treated patient populations.

Furthermore,.the lower limit of 95% confidence interval of treatment difference might be too large to make conclusion that E-TRANS (fentanyl) treatment is therapeutically equivalent to an IV PCA morphine regimen.

In conclusion, Study C-2001-011 showed superiority of the E-TRANS (fentanyl) compared to placebo. The results have been replicated in the Study C-95-016.

6. Appendix

Table 1 Demographic and Baseline Characteristics by Treatment Group --- C-2001-011

	Treated Patients		
Characteristic	E-TRANS (fentanyl) 40 µg (n=244)	Placebo (n=240)	p-value
Gender			0.7799
Male	74 (30%)	70 (29%)	
Female	170 (70%)	170 (71%)	
Race			0.5212
Caucasian	205 (84%)	207 (86%)	
Black	23 (9%)	17 (7%)	
Asian	5 (2%)	2 (1%)	
Hispanic	9 (4%)	13 (5%)	
Other	2 (1%)	1 (0.4%)	
Age (yr)			
Mean (SD)	54.0 (14.8)	53.1 (14.4)	0.5105
Height (cm)			
N	243	240	
Mean (SD)	167.0 (10.1)	168.1 (8.8)	0.1998
Weight (kg)			
Mean (SD)	80.8. (18.4)	81.8 (19.6)	0.5885
Body Mass Index			0.8101
n	243	240	
Mean (SD)	29.0 (6.4)	28.9 (6.5)	
Surgery Type			0.4764
Lower Abdominal	121 (50%)	115 (48%)	
Orthopedic Bone	113 (46%)	110 (46%)	
Thoracic	6 (3%)	7 (3%)	
Upper Abdominal	3 (1%)	8 (3%)	
Upper Abdominal, Lower Abdominal	1 (0.4%)		
Post-Operative ASA Physical Status			0.0904
I	25 (10%)	30 (13%)	
II	175 (72%)	150 (63%)	
III	44 (18%)	60 (25%)	

P-value was calculated using ANOVA for numerical data, chi-square test for categorical data.
Copied from Tables 11.3.1.1, 11.3.1.2-2, 11.3.1.2-3

Table 2 Demographic and Baseline Characteristics by Treatment Group --- C-2000-008

	Treated Patients		
Characteristic	E-TRANS (fentanyl) 40 µg (n=154)	Placebo (n=51)	p-value
Gender			0.8396
Male	46 (30%)	16 (31%)	
Female	108 (70%)	35 (69%)	
Race			0.6600
Caucasian	125 (81%)	45 (88%)	
Black	17 (11%)	5 (10%)	
Asian	1 (0.6%)	0	
Hispanic	10 (7%)	1 (2%)	
Other	1 (0.6%)	0	
Age (yr)			
Mean (SD)	51.1 (15.1)	51.7 (15.4)	0.8209
Height (cm)			
Mean (SD)	168.4 (9.1)	168.1(9.7)	0.8011
Weight (kg)			
Mean (SD)	79.0 (18.5)	80.3 (16.0)	0.6487
Body Mass Index			0.5448
Mean (SD)	27.8 (6.3)	28.4 (5.1)	
Surgery Type			0.8718
Lower Abdominal	80 (52%)	26 (51%)	
Orthopedic Bone	54 (35%)	20 (39%)	
Thoracic	2 (1%)	0 (0%)	
Upper Abdominal	17 (11%)	5 (10%)	
Upper Abdominal, Lower Abdominal	1 (0.6%)	0 (0%)	
Post-Operative ASA Physical Status			0.5052
I	25 (16%)	6 (12%)	
II	98 (64%)	37 (73%)	
III	31 (20%)	8 (16%)	

P-value was calculated using ANOVA for numerical data, chi-square test for categorical data.
Copied from Tables 11.3.1.1, 11.3.1.2-2, 11.3.1.2-3

Table 3 Demographic and Baseline Characteristics by Treatment Group --- C-95-016

Characteristic	Treated Patients: E-TRANS (fentanyl) 40 µg (n=77)	Treated Patients: Placebo (n=25)	p-value
Gender			0.4712
Male	14 (18%)	3 (12%)	
Female	63 (82%)	22 (88%)	
Race			0.7050
Caucasian	62 (81%)	19 (76%)	
Hispanic	1 (1%)	0 (0%)	
Other	14 (18%)	6 (24%)	
Age (yr)			
Mean (SD)	45.6 (11.6)	43.4 (11.1)	0.4188
Height (cm)			
n	76	25	
Mean (SD)	165.6 (8.3)	165.4 (9.3)	0.9470
Weight (kgs)			
Mean (SD)	75.0 (14.7)	71.8 (12.8)	0.3232
Body Mass Index			0.2793
n	76	25	
Mean (SD)	24.4 (4.8)	26.2 (4.3)	
Surgery Type			0.2434
Lower Abdominal	58 (75%)	18 (72%)	
Orthopedic Bone	16 (21%)	6 (24%)	
Upper Abdominal	3 (4%)	0 (0%)	
Other		1 (4%)	
Post-Operative ASA Physical Status			0.4500
I	56 (73%)	21 (84%)	
II	19 (25%)	4 (16%)	
III	2 (3%)	0 (0%)	

P-value was calculated using ANOVA for numerical data, chi-square test for categorical data.
Copied from Tables 6.1.1, 6.1.4.2, 61.4.4

Table 4 Demographic and Baseline Characteristics by Treatment Group --- C-2000-007

	Treated Patients		
Characteristic	E-TRANS (fentanyl) 40 µg (n=316)	IV PCA Morphine (n=320)	
Gender			0.5863
Male	87 (28%)	82 (26%)	
Female	229 (73%)	238 (74%)	
Race			0.8036
Caucasian	233 (74%)	234 (73%)	
Black	55 (17%)	62 (19%)	
Asian	3 (1%)	4 (1%)	
Hispanic	22 (7%)	16 (5%)	
Other	3 (0.9%)	4 (1%)	
Age (yr)			
Mean (SD)	51.2 (15.3)	50.2 (14.8)	0.4040
Height (cm)			
Mean (SD)	166.7 (9.1)	166.9 (9.5)	0.7364
Weight (kg)			
Mean (SD)	81.1 (20.7)	81.8 (20.2)	0.6516
Body Mass Index			0.6104
Mean (SD)	29.1 (6.8)	29.3 (6.8)	
Surgery Type			0.9461
Lower Abdominal	182 (58%)	190 (59%)	
Orthopedic Bone	116 (37%)	111 (35%)	
Upper Abdominal	12 (4%)	13 (4%)	
Thoracic	4 (1%)	5 (2%)	
Upper Abdominal, Lower Abdominal	2 (0.6%)	1 (0.3%)	
Post-Operative ASA Physical Status			0.8493
I	56 (18%)	52 (16%)	
II	214 (68%)	218 (68%)	
III	46 (15%)	50 (16%)	

P-value was calculated using ANOVA for numerical data, chi-square test for categorical data.
Copied from Tables 11.3.1.1, 11.3.1.2-2, 11.3.1.2-3

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