SYNOPSIS

NAME OF SPONSOR/COMPANY: Janssen-Cilag EMEA NAME OF FINISHED PRODUCT: - NAME OF ACTIVE INGREDIENT(S): Fentanyl (R004263)	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Protocol No.: FEN-PPA-401
Title of Study: Comparison of Transdermal Fentanyl PCA and IV Morphine PCA in the Management of Post-Operative Pain Control.

Principal Investigator: Stefan Grond, M.D. – University of Halle [redacted], Germany

Publication (Reference): JRF, Clinical Research Report FEN-PPA-401_EU, 30 May 2007 (EDMS-PSDB-6251374:2.0)

Study Initiation/Completion Dates: 14 June 2004 / 19 July 2005 | **Phase of development:** IIIB

Objectives:

The primary objective of this study was to evaluate the clinical use of E-TRANS® fentanyl treatment and intravenous (IV) morphine patient-controlled analgesia (PCA) treatment for the management of moderate to severe post-operative pain in subjects who had undergone an elective major abdominal or orthopedic surgical procedure. The study was designed to demonstrate non-inferiority of E-TRANS® fentanyl versus IV morphine PCA treatment in Subject's Global Assessment (SGA) of method of pain control during the first 24 hours post-surgery.
Secondary objectives were: to assess pain control in both treatment groups, including the SGA and Investigator's Global Assessment (IGA); to compare the safety of E-TRANS® fentanyl for pain management in this surgical population with the safety of IV morphine PCA; to explore the impact on care procedures of the E-TRANS® fentanyl system and the IV morphine PCA device, by means of validated Ease-of-Care (EoC) Questionnaires, related to the subject, nursing staff and physical therapists; to compare technical issues with both systems.

Methodology: This was an international, multicenter, randomized, open-label, active comparator, parallel-group study.

Number of Subjects (Planned and Analyzed): planned: 650 subjects
analyzed: 660 ("*all subjects*" population)
652 ("*intent-to-treat*" population)
619 ("*per-protocol*" population)

Diagnosis and Main Criteria for Inclusion: expected moderate to severe post-operative pain after elective major abdominal or orthopedic surgery.

- Adult, age 18 or older, male or female;
- American Society of Anesthesiology (ASA) pre-operative physical status I, II, or III;
- If the subject was female and of childbearing potential, she had to have a negative pregnancy test after hospital admission, unless the subject had undergone a hysterectomy;
- Subjects, after an elective major abdominal or orthopedic surgical procedure, who were expected to have moderate or severe pain requiring parenteral opioids for at least 24 hours after surgery; the orthopedic procedure could involve lower extremities, shoulder and back bone;
- Subjects who were capable of understanding and cooperating with the requirements of the study and operating the E-TRANS® fentanyl system or the morphine IV PCA device;
- Subjects who had signed and dated an informed consent to participate in the study during the pre-operative assessment;
- Subjects who had been admitted to the recovery room after general anesthesia, spinal anesthetic of ≤ 4 hours duration of action or epidural anesthesia after an elective major abdominal or orthopedic surgical procedure and who would expectedly suffer from moderate to severe pain and would require post-operative analgesia for at least 24 hours. Subjects with epidural or regional anesthesia were only included if the provided analgesia was short lasting and was only given for the period of surgery and not for the period in the recovery room. When entering the recovery room, subjects with epidural or regional anesthesia had to still qualify for needing IV PCA analgesia according to the local hospital standards;

SYNOPSIS (CONTINUED)

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Diagnosis and Main Criteria for Inclusion (continued):

- Subjects who were alert and breathing spontaneously for at least 30 minutes in the waking room (recovery); respiratory rate 10 to 24 breaths per minute; oxygen saturation ≥ 90% (with or without supplemental oxygen); subjects had to be able to answer questions and follow commands;
- Subjects with a pain score ≤ 4 out of 10 on a Numerical Rating Scale (NRS) after titration to comfort with IV morphine. In case of abdominal surgery, this had to be measured 5 minutes after deep breathing and coughing;
- Subjects who were expected to remain hospitalized for at least 24 hours post-operatively.

Test Product (Fentanyl), Dose and Mode of Administration, Batch No.:

Fentanyl; 40 µg fentanyl per on-demand dose, delivered over 10 minutes with a maximum of 6 doses/hr (240 µg/hr) for 24 hours or a maximum of 80 doses (3.2 mg);

Fentanyl HCl Subject-Controlled Transdermal System
(Transdermal Subject-Controlled Analgesia – E-TRANS® fentanyl);

Batch no: 0330669 and 0430235.

Reference Therapy (Morphine), Dose and Mode of Administration:

On demand doses with a maximum of 20 mg/2 hr (240 mg during 24 hours);

IV Subject-Controlled Analgesia (IV morphine PCA).

Duration of Treatment: at least 24 hours and maximum 72 hours

Analysis Populations: "*per-protocol*" population as primary efficacy population for non-inferiority; "*intent-to-treat"* population as secondary, confirmatory population for efficacy analyses; "*all subjects*" population for general and safety analyses.

Key Study Procedures

- Informed Consent
- Medical and Surgical History
- Physical Examination
- Pregnancy Test
- Eligibility criteria
- Randomization
- Administration of Study Drug
- Pain Intensity Rating (using a 10-point numerical scale)
- Subject and Investigator Global Assessments (SGA and IGA)
- Application Site Reactions, Non-Routine Events and System Adherence (E-TRANS® fentanyl)
- Subject, Nurse and Physical Therapist Ease-of-Care (EoC) Questionnaires
- Recording of Concomitant Medications
- Recording of Adverse Events
- Evaluation for Clinically Relevant Respiratory Depression
- Glasgow Coma Scale

SYNOPSIS (CONTINUED)

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Baseline Characteristics - Subject Disposition (Population: All Subjects)	**E-TRANS® fentanyl (N=325)**	**IV morphine PCA (N=335)**
Subjects Randomized (M/F; %)	43/57	43/57
Age (years): Mean (SEM)	53.5 (0.81)	53.0 (0.80)
Median (range)	53.0 (22-89)	53.0 (20-88)
Discontinuation of Treatment, n (%)	37 (11.4)	37 (11.0)
Reason, n (%)		
- Insufficient efficacy	9 (2.8)	5 (1.5)
- Insufficient tolerability	11 (3.4)	16 (4.8)
- Insufficient efficacy and insufficient tolerability	1 (0.3)	2 (0.6)
- Other medical event	6 (1.8)	5 (1.5)
- Rescue medication after first 3 hours	2 (0.6)	2 (0.6)
- Use of disallowed medication	0	1 (0.3)
- Inadequate analgesia	1 (0.3)	1 (0.3)
- Withdrawal of consent	1 (0.3)	2 (0.6)
- Technical failure twice in 24 hours	1 (0.3)	0
- Other	5 (1.5)	3 (0.9)
Efficacy (Population: Per-Protocol)	**E-TRANS® fentanyl (N=309)**	**IV morphine PCA (N=310)**
Primary Variable		
- **Subject Global Assessment of Method of Pain Control at 24h**	The proportions of "successes" in the per-protocol population on the SGA of the method of pain control at 24 hours were 88% and 89% in the E-TRANS® fentanyl and IV morphine PCA groups, respectively (p = 0.625). The 95% confidence interval for the difference in "success" rate was (-6.0%, 4.0%). Therefore, the trial met its primary endpoint by demonstrating non-inferiority of E-TRANS® fentanyl compared to IV morphine PCA. The proportions of "successes" were similarly high for the ITT population: p = 0.798, 95% CI (-5.2%, 4.8%).	
Secondary Variables		
- **Subject Ease-of-Care Questionnaire**	Subject's ratings of "Overall Ease-of-Care" were significantly higher in the E-TRANS® fentanyl compared to the IV morphine PCA group (4.3 [0.03] vs. 4.1 [0.03], p < 0.001). The differences between treatment groups reached statistical significance favoring E-TRANS® fentanyl for the individual subscales "Confidence with Device" (p = 0.016) and "Mobility" (p < 0.001). Importantly, the individual questions dealing with the technical aspects of using the E-TRANS® fentanyl system suggest that subjects found the device at least as easy, if not easier, to use than an IV morphine PCA.	

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Efficacy, Secondary Variables, cont'd		
- **Nurse Ease-of-Care Questionnaire**	Nurses' ratings on the "Overall Ease-of-Care" were significantly more favorable (i.e., the means were lower) for E-TRANS® fentanyl vs. IV morphine PCA (0.7 [0.04] vs. 1.2 [0.05], $p < 0.001$). All 3 nurse subscales were also individually significantly different, favoring E-TRANS® fentanyl vs. IV morphine PCA ($p < 0.001$). The subset of nurses who cared for both E-TRANS® fentanyl and IV morphine PCA subjects (n= 143), significantly favored E-TRANS® fentanyl over IV morphine PCA on all subscales.	
- **Physical Therapist Ease-of-Care Questionnaire**	Physical therapists' ratings on the "Overall Ease-of-Care" were significantly more favorable (i.e., the means were lower) for E-TRANS® fentanyl vs. IV morphine PCA (0.5 [0.05] vs. 0.7 [0.06], $p < 0.001$). All 3 physical therapist subscales were also individually significantly different, favoring E-TRANS® fentanyl vs. IV morphine PCA ($p \leq 0.021$). The subset of physical therapists who cared for both E-TRANS® fentanyl and IV morphine PCA subjects (n= 39), significantly favored E-TRANS® fentanyl over IV morphine PCA on all subscales ($p \leq 0.001$), except not on "Satisfaction" ($p = 0.094$).	
- **Subject Global Assessment of Method of Pain Control at 48h, 72h and Last Assessment**	The "success" rates of the two PCA systems by SGA at 48 hours, 72 hours, and at last assessment were similarly high in subjects receiving E-TRANS® fentanyl and IV morphine PCA. A greater proportion of subjects rated E-TRANS® fentanyl vs. IV morphine PCA as "excellent" at 24 hours (39.2% vs. 29.7%). At the last assessment, SGA scores were significantly different (3.4 [0.04] vs. 3.2 [0.04], E-TRANS® fentanyl vs. IV morphine PCA, respectively, $p = 0.002$).	
- **Investigator Global Assessment at 24h, 48h and 72h**	The "success" rates of the two PCA systems by IGAs were similarly high in the E-TRANS® fentanyl and IV morphine PCA groups at 24 hours (92.2% and 91%, respectively, $p = 0.585$). IGAs success rates at 48 hours, 72 hours, and at last assessment were similar in subjects receiving E-TRANS® fentanyl and IV morphine PCA. A greater proportion of investigators rated E-TRANS® fentanyl vs. IV morphine PCA as "excellent" at 24 hours (46.6% vs. 25.5%) and at the last assessment (56.6% vs. 31.0%, respectively). These differences paralleled significant differences in IGA scores at 24 hours (3.4 [0.04] vs. 3.2 [0.03], $p < 0.001$) and at the last assessment (3.4 [0.04] vs. 3.2 [0.04], respectively, $p < 0.001$), in the E-TRANS® fentanyl vs. IV morphine PCA groups, respectively.	
- **Pain Intensity**	From a mean (SE) post-operative pain intensity score at Time 0 (the time of application of PCA or following titration to comfort) of 3.0 [0.07] and 3.1 [0.06] in the E-TRANS® fentanyl and IV morphine PCA groups, respectively. Pain intensity decreased to similar values in the two treatment arms at 24 hours (2.5 [0.10] and 2.4 [0.11], respectively (95% CI:-0.19, 0.39) and at the last study observation (1.8 [0.10] and 1.8 [0.10], respectively (95% CI: -0.28, 0.28) in the per-protocol population. The findings in the ITT population were virtually identical.	

SYNOPSIS (CONTINUED)

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Efficacy, Secondary Variables, cont'd		
- **Trial Termination**	The proportion of subjects completing the trial was similar in the E-TRANS® fentanyl and IV morphine PCA groups, 90.3% and 90.6%, respectively. The proportion of subjects completing the trial according to the various completion criteria were as follows: completion of 72 hours of study treatment (36.0%), no longer requiring opioid analgesia before 72 hours (36.8%), switched over to other (oral) analgesia before 72 hours (15.3%), and hospital discharge before 72 hours (2.3%). More E-TRANS® fentanyl subjects (44.7%) completed 72 hours of study treatment than did IV morphine PCA subjects (27.4%). Amongst subjects discontinuing early from the trial, reasons for termination were similar between treatment arms.	
- **On-Demand E-TRANS® Fentanyl or IV Morphine PCA Doses**	The mean (SEM) number of on-demand E-TRANS® fentanyl doses was 47.4 (2.02) for the per-protocol population. The majority of the subjects (51.8%) received between approximately 11 and 50 doses (median 38.0, range 3-168). Subjects remaining on E-TRANS® fentanyl at 24 hours of the study (n = 298) used a mean (SEM) of 24.5 (0.97) estimated doses. For those sites whose IV morphine PCA protocol is known, the on-demand doses ranged from 1-3 mg across sites with lockout periods between 5-20 minutes. The mean (SEM) amount of morphine delivered from IV PCA was 55.1 (2.74) mg for the per-protocol population. The majority of the subjects (48.6%) received between approximately 11 and 50 mg morphine (median 42.0, range 0-278). Subjects remaining on IV morphine PCA at 24 hours (n = 296) used a mean (SEM) of 34.4 (1.45) mg.	
- **Rescue Medication**	A similar proportion of E-TRANS® fentanyl and IV morphine PCA subjects were treated with rescue medications anytime during study drug treatment (10.7% vs. 9.7%, 95% CI: -5.8%, 3.8% for difference). Both the number of doses of rescue morphine and quantity of rescue morphine was similar in the two treatment groups. The number of doses of rescue morphine in the E-TRANS® fentanyl and IV morphine PCA groups were median 1.0 in each group. The median quantity of rescue morphine used was 5.0 mg in both groups.	
- **Use of Anti-Emetics**	The use of anti-emetic medication was similar between E-TRANS® fentanyl and IV morphine PCA treatment groups. The most commonly used anti-emetics were included in the non-analgesics class (metoclopramide and ondansetron).	
- **Non-opioid Analgesics**	A similar proportion of E-TRANS® fentanyl and IV morphine PCA subjects received non-opioid analgesics after enrollment. The most commonly used non-opioid analgesics were paracetamol and the NSAIDs diclofenac and metamizole.	
- **Suspected Technical Failures of the E-TRANS® Fentanyl Systems or IV Morphine PCA Devices**	In the all subjects population, suspected device malfunctions or failures were reported in 33 of 325 subjects randomized to E-TRANS® fentanyl (10.2%) and this number included suspected failures observed prior to application of the system. The proportion of devices with suspected failures was 34 out of 756 (4.5%).	

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Efficacy, Secondary Variables, cont'd		
- **Assessment of the Adherence of the E-TRANS® Fentanyl System**	The vast majority of E-TRANS® fentanyl systems (652 of 731, 89.2%) adhered to at least 90% of the area with no unattached edges. In 23 of the 731 systems used (3.1%), tape was required to secure it.	

Additional analyses of efficacy parameters were performed on the following subpopulations:

- by surgery type: back bone, hip, knee, lower abdominal, upper abdominal and pelvic surgery
- by gender: male and female
- by ASA physical status: ASA I, ASA II and ASA III physical status
- by anesthesia type: spinal and general anesthesia
- by country (only for Germany, France and the United Kingdom).

For the results of these additional analyses, please refer to the report body.

Safety (Population: All subjects)	**E-TRANS® fentanyl** **(N=325)**	**IV morphine PCA** **(N=335)**
Adverse Events (AE), n (%)		
Most frequently reported AEs (≥5%)		
Nausea	137 (42.2)	159 (47.5)
Vomiting	55 (16.9)	50 (14.9)
Application site erythema	122 (37.5)	0
Application site pruritus	23 (7.1)	0
Application site vesicles	20 (6.2)	0
Dizziness	13 (4.0)	20 (6.0)
No. (%) with one or more AE	243 (74.8)	211 (63.0)
No. (%) of deaths	0	1 (0.3)
No. (%) with one or more serious AE	10 (3.1)	10 (3.0)
No. (%) treatment stopped due to AE	18 (5.5)	23 (6.9)
Deaths	One subject (in the IV morphine PCA arm) died of progressive brain metastasis and hypertensive encephalopathy. There were no deaths in the E-TRANS® fentanyl arm.	
Application Site Reactions and Infusion Site Reactions	Application site reactions (the vast majority of which were erythema) were reported in 144 E-TRANS® fentanyl subjects (44.3%). In all but 7 subjects, the reactions were of mild or moderate severity. A small number of subjects had application site blistering-type reactions (coded as "vesicles") (n = 20), edema (n = 10), or pruritus (n = 23). Infusion site reactions were reported in 22 IV morphine PCA subjects (6.6%), all of which were of mild or moderate severity.	
Clinically Relevant Respiratory Depression	Only one subject randomized to the IV morphine PCA group and no subjects in the E-TRANS® fentanyl group experienced Clinically Relevant Respiratory Depression (bradypnea with respiratory rate < 8 and excessive sedation).	
Oxygen Saturation	A single minimum oxygen saturation value of < 88% was recorded in 10 (3.1%) E-TRANS® fentanyl compared to in 19 (5.7%) IV morphine PCA subjects.	

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Safety, continued		
Vital Signs	Mean and median heart rate and blood pressure were similar between the two treatment groups at all study time points. There were very few episodes of two consecutive systolic or diastolic blood pressure or heart rate values outside either the lower or upper limits of normal in the same direction in both treatment groups.	

Additional analyses of safety parameters were performed on the following subpopulations:

- by surgery type: back bone, hip, knee, lower abdominal, upper abdominal and pelvic surgery
- by gender: male and female
- by ASA physical status: ASA I, ASA II and ASA III physical status
- by anesthesia type: spinal and general anestheasia
- by subjects who only used opioids and subjects who used opioids and non-opioid analgesics (only AEs as safety parameter were analyzed).
- by country (only for Germany, France and the United Kingdom).

For the results of these additional analyses, please refer to the report body.

Conclusions

This large, multicenter, randomized, open-label, active-controlled trial demonstrated that as a method of pain control as assessed by Subject Global Assessments, E-TRANS® fentanyl is non-inferior to IV morphine PCA, administered in a fashion reflective of clinical practice. Findings from the secondary efficacy endpoints including pain intensity and Investigator Global Assessment scores from 24 to 72 hours, and Subject Global Assessment scores at later time points (48 and 72 hours) were consistent with the primary endpoint. Furthermore, efficacy of E-TRANS® fentanyl was demonstrated despite a background of non-opioid analgesic medication use throughout the study treatment phase.

The simplicity of the operation of the E-TRANS® fentanyl system was evident in the responses of the study's post-operative subject population on the validated "Ease-of-Care" subject questionnaires. These data suggest that despite the novelty of the E-TRANS® system, subjects were able to easily grasp the use of the device and to successfully and confidently self-administer the drug.

There were no episodes of CRRD in subjects receiving E-TRANS® fentanyl. Additionally, adverse events potentially related to CNS depression (somnolence, confusion and CNS depression), respiratory depression (hypoxia, hypoventilation, and apnea), hypotension, and urinary retention occurred uncommonly, but numerically more often with IV morphine PCA than with E-TRANS® fentanyl. Application site reactions (mostly erythema and largely of mild to moderate severity) were common; however, application site reactions resulted in discontinuation of treatment in only 3 subjects. A small number of subjects had application-site blistering-type reactions (coded as "vesicles") (n = 20), edema (n = 10), or pruritus (n = 23). The safety of the E-TRANS® fentanyl system was characterized against a backdrop of recently administered intra-operative analgesics, anesthetics, and muscle relaxants and use of non-opioid analgesic and non-opioid CNS depressant drugs administered according to clinical need. Additionally, subjects with a variety of common surgical procedures (including abdominal, pelvic, and orthopedic surgeries) were safely treated with E-TRANS® fentanyl.

In conclusion, E-TRANS® fentanyl was demonstrated to be at least as well tolerated as IV morphine PCA. Further, the usage of the device was considered to be easy by subjects and less bothersome and time-consuming by both physical therapists and nurses.

Date of the report: 30 May 2007

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