SYNOPSIS

Name of Sponsor/Company: JANSSEN-CILAG, S.A.	
Name of Finished Product: Fentanyl	
Name of Active Ingredient(s): Fentanyl	
Protocol number: CR003526 **Title of study:** A randomized study to assess the efficacy and safety of fentanyl-TTS versus minor opioids in patients with moderate to severe chronic oncological pain previously treated with NSAIDs.	
Investigators: Main investigator: Dr. Javier Cevas Chopitea (Hospital de La Rioja, Logroño. Spain)	
Study centre(s): 6 centers from all over the national territory (Spain)	
Publication (reference): N/A	
Study period (years): Date of first patient in: 05/12/2003 Date of last patient out: 27/02/2005	**Phase of development:** IV

Objectives:

- To show, using the analgesic WHO scale, that fentanyl-TTS may be directly used for treating moderate to severe cancer pain in patients treated with NSAIDs, acetaminophen, or metamizole (first step drugs) avoiding the second step, and may be at least as effective and safe as currently used second step drugs, minor opioids.
- To assess the advantages of this treatment regimen for patients with cancer pain.

Methodology:

A multicenter, randomized, open-label, nationwide study.

The patients meeting the inclusion and exclusion criteria were randomized to treatment with fentanyl-TTS (experimental drug) or with minor opioids (control arm).

The follow-up was two months, during which controls were performed every 7 days, except for the first that was on Day 4 (with optional phone follow-up or at the clinic, but with at least 3 pre-established visits, baseline, Day 30 and Day 60 at the clinic).

If pain was not controlled (VAS$\leq$3), the investigator could increase the dose of the relevant drug (according to data sheet).

Number of patients:

Planned: 112

Included: 19 (9 patients with fentanyl-TTS and 10 patients with tramadol. 2 patients were excluded)

Analysed: 17 (8 in the experimental arm (fentanyl-TTS) and 9 in the control arm (tramadol))

Diagnosis and main criteria for inclusion:

- Men and women aged 18 years or older.
- Moderate to severe chronic pain due to the oncological disease (VAS$\geq$5) treated with first-step drugs: NSAID, paracetamol or metamizole.
- Confirmed diagnosis of cancer.
- Patients not treated with opioids in the previous two months.
- Signed informed consent.
- No pain with neuropathic component.
- No patients with dermatological disease, hypersensitivity to fentanyl.
- No patients with cardiac, respiratory or CNS history.
- No pregnant women or women of child-bearing age using no contraceptive methods.

Test product, dose and mode of administration:

Durogesic®, dosage forms of 25µg/h, 50µg/h and 100µg/h. Transdermal patches

Duration of treatment: 2 months.

Reference therapy, dose and mode of administration:

Tradonal® retard (tramadol), dosage forms of 100mg, 150mg and 200mg, Oral administration.

Contugesic® (dihydrocodeine), dosage forms of 60mg, 90mg and 120mg. Oral administration.

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Criteria for evaluation:

Visit number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**
Day of treatment	**Day 0**	**Day 3***	**Week 2***	**Week 3***	**Week 4**	**Week 5***	**Week 6***	**Week 7***	**Week 8**
Days of telephone call/consultation*	**Con.**	**x**	**x**	**x**	**Con.**	**x**	**x**	**x**	**Con.**
Informed consent	**x**								
Demographic data	**x**								
Physical examination	**x**								
Medical/surgical history	**x**								
Cancer disease data	**x**								
Analgesic regimen in the past 7 days	**x**								
Assessment of type of pain	**x**								
Assessment of control of pain VAS	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**
Assessment of adjustment of medication dosage		**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**
Side effects of analgesic treatment		**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**
Treatment assessment questionnaire (patient)					**x**				**x**
Adverse events		**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**
Concomitant medication	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**
Trial medication	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**
Rescue medication	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**

*Calls or visits were made at the clinic to assess whether the patient needed increased doses for analgesia.
V2: For patients in the arm corresponding to fentanyl patches, this visit should coincide with the change of patch so that the dose could be increased if necessary.
The weekly visits/calls should be performed the same day of the week as Visit 1 (e.g. every Tuesday).
Note: Doses could be increased at any time during the trial (regardless of visits). Patients were given a card with a telephone number they could call between visits, if so required. All contact of the patient with the physician, other than the study visits, have been entered in the CRF.
The visits have a window period of 1 day, except for the first visit. The day of the first visit must be the same the first patch change.

Efficacy:

The primary endpoint has been the control of pain during treatment. Pain was assessed by the visual analogue scale. Pain severity was assessed at each follow-up visit.
Efficacy was defined by the number of points reduced in the severity of pain in the VAS scale at each visit.

Secondary endpoints

To assess the advantages of using fentanyl-TTS after the first step of the WHO analgesic ladder as compared to minor opioids. This advantages were assessed based on:

Safety:

- Incidence of side effects associated with treatment with opioids during treatment. The following was assessed by a table with the most common side effects: nausea, vomiting, constipation and drowsiness (WHO) and their severity.
- Quantity of support drugs required by the patients to cope with the side effects occurring.
- Adverse events related to the study drug.
- Percentage of patients discontinuing or switching treatment due to side effects.

Statistical methods:

Data analysis was performed by intention-to-treat for both efficacy and safety.
The quantitative variables were described by the mean, median, standard deviation, minimum, maximum and 95% CI. The qualitative variables were represented by absolute and relative frequencies.
Efficacy: The primary objective (pain assessment) has provided the number and percentage of patients obtaining VAS ≤ 3 at the end of the study; comparison between the two groups by Chi-squared or Fisher test.

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The dose increases and decreases were calculated for both treatment groups and compared by the Student's test for independent groups.
Safety: incidence of general adverse events and expected adverse events.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:
Primary efficacy endpoints

The primary efficacy endpoint was pain assessment by comparing between the two treatment groups the proportion of patients who achieved a VAS score ≤ 3 at study end or at the last visit with data. Results were as follows:

VAS	Fentanyl-TTS			Minor opioid		
	n	%	95% CI	n	%	95% CI
≤ 3	4	80.0	28.4 – 99.5	9	100.0	66.4 – 100.0
> 3	1	20.0	0.5 – 71.6	-	-	0.0 – 33.6
Total	5	100.0		9	100.0	

No statistically significant differences were found between the groups in pain recovery as measured by VAS (Fisher's exact test, $p = 0.357$).

Secondary efficacy endpoints

Dose increases
Mean number of dose increases were 1.1 increases in the fentanyl-TTS group and 0.6 increase in the minor opioid group. In total, 50% of the patients on fentanyl-TTS and 33.3% of patients on minor opioids increased the dose.
The mean number of dose increases in each treatment group was as follows:

Dose increases	Fentanyl-TTS		Minor opioid	
	n	%	n	%
0	4	50.0	6	66.7
1	1	12.5	1	11.1
2	1	12.5	2	22.2
3	2	25.0	-	-
Total	8	100.0	9	100.0

Dose decreases occurred in two patients in the fentanyl-TTS group.

In the group on minor opioids, 2 patients reached the maximum permitted dose of tramadol (400mg). In the group on fentanyl-TTS, 1 patient reached the maximum dose permitted 100µg/h.
Rescue medication requirements
All patients required rescue medication at some point during the study.

Patients from the minor opioid group who required a switch in medication and were changed to the fentanyl-TTS group
Of the 9 patients in the minor opioid group, only one of them (11.1%) was switched to fentanyl-TTS treatment at visit 8 (95% CI: 0.0% - 36.7%).
Patient assessment of analgesic treatment
Patient assessment of the analgesic questionnaire was generally positive in both treatment groups at both visits 5 and 9.

SAFETY RESULTS:

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General unexpected adverse events
Sixteen general AEs were recorded, 11 AEs in the fentanyl-TTS group and 5 AEs in the minor opioid group. Twelve AEs were mild-moderate and 4 severe, 3 of them in the fentanyl-TTS group and 1 of the group on minor opioids. In no case in the group on minor opioids was it necessary to adopt any measures for the study drug and in 5 AEs of the fentanyl-TTS group the drug was definitively discontinued. 11 SAEs were considered to be drug-related, 9 and 2 in the groups on fentanyl-TTS and minor opioids, respectively. Three AEs of the fentanyl-TTS group were serious and in two of them hospitalization was required.

Expected and related adverse events (CRF form)
There were 55 expected AEs, 27 AEs in the fentanyl-TTS group and 28 AEs in the minor opioid group.

In total, 7 patients had serious complications during the study, 2 died for causes unrelated to the drug (one from each group), 3 patients were hospitalized for adverse events, in two cases for reasons related to the drug: constipation and vomiting (fentanyl-TTS and minor opioids, respectively), and in 1 case for ascitis not related to the study drug (fentanyl-TTS), 1 patient had serious severe asthenia not requiring hospitalization (fentanyl-TTS) and 1 patient had multiple AEs (fentanyl-TTS). All patients, except for one that completed the treatment per protocol, discontinued the protocol: 5 patients because of complications and 1 patient because of withdrawal of consent.

CONCLUSION:
To sum up, despite the small patient sample of the trial, the results suggest that fentanyl-TTS is at least as effective and safe as minor opioids in the treatment of moderate to severe chronic oncological pain.

Date of the report: 13 December 2006 (final correction 16 march 2007)

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