SYNOPSIS

Trial identification

Company: JANSSEN PHARMACEUTICA N.V. **Finished product**: Durogesic ™ **Active ingredient**: Fentanyl (R004263)		
Title: Randomized, double-blind, placebo-controlled, parallel-group, multicentre trial to investigate Durogesic™ in comparison to placebo in subjects with moderate to severe pain induced by osteoarthritis of the hip or the knee, who are in need of and waiting for hip or knee replacement.	**Trial No**.: CR003004 **Clinical phase**: IV	
Investigator: Langford Richard, M.D., St Bartholomew's Hospital, West Smithfield, London EC1A 7BE, UK	**Country**: international	
Reference: J-C EMEA, Clinical Research Report CR003004, October 2004 (EDMS-PSDB-3850522)		
Trial period: Start: 29 May 2002 End: 28 April 2004	**No. of investigators**: 19 **No. of subjects screened**: 553 **No. of subjects randomized**: 416	

Protocol summary

Indication: osteoarthritis

Primary objective:

- To establish the superior analgesic effect of Durogesic over placebo in patients with osteoarthritis pain, inadequately controlled by weak opioids, mostly in combination with non-opioid analgesics. The difference in pain relief over time, between baseline and end point, assessed by Visual Analogue Scales (VAS) by means of a pain diary, was compared in the two groups as average area under the curve.

Secondary objectives:

- To compare other pain-related data during treatment with Durogesic versus placebo, obtained by means of the pain diary and pain assessment questionnaires.
- To explore the possible impact on functionality and quality of life of Durogesic vs placebo.
- To identify potential issues related to opioid treatment discontinuation.
- To explore the degree to which Durogesic provides adequate pain relief with an acceptable side-effect profile in patients with pain that might vary in intensity during the day.
- To assess the safety of Durogesic in osteoarthritis (OA) patients.

Trial design: randomized, double-blind, placebo-controlled, parallel-group, multicentre, prospective trial

Inclusion criteria:

1. Subjects older than 40 years of age.
   At baseline, female subjects of childbearing potential had to be using adequate contraception (i.e., using oral or IM contraception or an IUCD) and had to have a negative urine pregnancy test. Postmenopausal female subjects had to have been amenorrhoeic for at least 1 year; in this case the pregnancy test was not required. Subjects who were breastfeeding were excluded.
2. Subjects gave written informed consent.
3. Subjects with OA of the hip or the knee (target joints) (defined by the American College of Rheumatology)+ radiological evidence of OA from the target joint recorded in the subject's (hospital) file.
   These subjects had to need and be waiting for hip or knee replacement surgery. This criterion also applied to subjects who refused such replacement surgery or who could not have it for medical reasons (in accordance with the criteria for exclusion from the waiting list for a hip or knee replacement).
4. Subjects who had chronic pain for more than 3 months for at least 20 days per month.

Inclusion criteria (cont'd):

5. Subjects with moderate to severe OA pain of the target joint, whose pain was not adequately controlled with weak opioids, with or without paracetamol, whether or not the subject was using these medications. This was defined as subjects with a mean VAS score equal to or greater than 50 (on a scale of 0-100) at the start of the Run-In Period (mean VAS score of the morning and evening assessment of question 1), at the end of the Run-In Period (mean VAS score of the morning and evening assessment of question 1 on Day –1) and over the whole Run-In Period.

Exclusion criteria:

1. Subjects who had previously failed Durogesic therapy or those who had previously discontinued Durogesic due to adverse events (AEs).
2. Subjects who had received treatment with a potent opioid in the 4 weeks preceding study entry.
3. History of allergy or hypersensitivity to fentanyl or to the adhesives in the system.
4. Subjects currently treated for depression or epilepsy (antidepressant and anti-epileptic medication are reported to have a potential supplementary analgesic effect or a potential synergistic effect when associated with opioids).
5. Subjects who had taken sedative hypnotics, anaesthetics and/or muscle relaxants in the week preceding the Run-In Period (exception: low dose sedative hypnotics with the sole purpose to help night rest were not excluded). Subjects who used a topical NSAID during the week before the Run-In Period were also excluded, unless the topical NSAID was already initiated at least one week pre-study and was continued at a stable dose throughout the study.
   Only in Canada: subjects who have taken sedative hypnotics, phenothiazines, tranquilizers, sedating antihistamines, anaesthetics and/or skeletal muscle relaxants in the week preceding the Run-In Period or during the study.
6. Subjects with documented or suspected alcohol or drug abuse, or who were suspected of having an addictive personality.
7. Subjects who were experiencing another type of continuous pain that stood out in comparison with OA pain (e.g. fibromyalgia).
8. Subjects to whom any of the following applied:
   - Major trauma to the target joints in the 6 months preceding study entry.
   - Infection in the target joints in the 6 months preceding study entry.
   - Apparent avascular necrosis in the target joints in the 6 months preceding study entry.
   - Intra-articular injections of corticosteroids in the target joints in the 2 months preceding study entry, or hyaluronan injections in the target joints in the 6 months preceding study entry.
9. Subjects who had major surgery in the 3 months preceding the study.
10. Subjects who had an arthrodesis in the year and/or arthroscopy in the 2 months preceding administration of study medication and/or arthrocentesis within 4 weeks of entry into the study.
11. Subjects who used a transcutaneous electrical nerve stimulation (TENS) machine in the 3 weeks preceding the Run-In Period.
12. Subjects who started any form of physiotherapy, massage or physical therapy in the 3 weeks preceding the Run-In Period. Such therapies could continue if they were started more than 3 weeks before the start of the Run-In Period and if they continued at the same frequency of administration throughout the study.
13. Subjects who underwent acupuncture in the 3 weeks preceding the double-blind phase.
14. Subjects for whom a treatment was planned within the study period that could alter the degree or nature of pain.

Exclusion criteria (cont'd):

15. Subjects known to have any of the following:
    - Bradycardia, chronic obstructive respiratory symptoms, susceptibility to present respiratory depression (possible synergistic effect associated with CNS drugs).
      Only in Canada: bradycardia (defined as a heart rate ≤ 60 bpm), chronic obstructive respiratory symptoms, susceptibility to present respiratory depression (includes sleep apnea or signs or symptoms suspicious of sleep apnea). There is a possible synergistic effect associated with CNS drugs.
    - Major motor impairment (including tremor) precluding the use of the pain diary.
    - Significantly abnormal renal or hepatic function.
    - Any disease or condition that compromised the function of those body systems that could result in altered absorption, excess accumulation, or impaired metabolism or excretion of the test medications.
    - A life-threatening disease.
    - A condition that in the investigator's judgement precluded participation in the study.
16. Subjects with a significant psychiatric disorder (including depression) or subjects receiving anti-psychotic medication.
17. Subjects who received an investigational drug or used an investigational device in the 30 days preceding study entry.
18. Subjects unable to comply with the study assessments and to complete the pain diary and/or the questionnaires.

Treatment		
Test products		
Form - dosing route	transdermal patches	
Medication	Placebo	Durogesic
Batch number	01I19/911, 02H12/413	01LB415, 02CB184, 02G19/341
Dosage	- starting dose: 1 patch (25µg/h) every 72h - titration in steps of 1 patch (25µg/h) every 72h until achievement of adequate pain control, with a maximum dose of 100 µg/h (4 patches) - patches are replaced every 72h	
Other trial medication		
Medication	Metoclopramide	Paracetamol[a]
Form - dosing route	10 mg tablets or equivalent formulation - oral	500 mg tablets or equivalent formulation – oral
Batch number	Commercial study medication was used for metoclopramide and paracetamol	
Dosage	prn	same as pretrial with a maximum of 4 g/day
Duration of treatment	6 weeks	
Duration of trial	Max 62 days (Run-In: 1 week; Treatment: 6 weeks; Tapering-Off: max 12 days)	
Disallowed medication	Chronically used steroidal drugs and/or anti-inflammatory analgesics were not allowed, unless started at least 1 week before study entry. In that case, they were continued during the trial, but the dosage had to be kept constant throughout the trial period. Subjects who were taking a weak opioid plus paracetamol during the Run-In Period, had to stop the weak opioid treatment at the time of randomization. Paracetamol treatment could be continued, but the dosage had to be kept constant throughout the trial period (with a maximum of 4 g per day).	

[a] paracetamol had to be provided because some patients were required to discontinue paracetamol/weak opioid combinations

Disallowed medication (cont'd)	Sedative hypnotics were excluded unless they had been started at least one week prior to entry in the study with the sole purpose of helping the subject's night rest. Each case had to be checked individually under supervision of the local country's medical monitor, to ensure that the dosage was in line with the exclusion criteria. No sedative hypnotics were allowed during the daytime[*].

Assessments

	Run-In	Treatment				Tapering off
		Uptitration period				
Visit number	V1[a]	V2	V3	V4	V5[b]	V6[c]
Treatment day	-7	1	15	29	43	46-49-52-55
Identification of target joint	X					
Eligibility confirmed	X	X				
Randomization		X				
Cessation of weak opioids		X				
Previous medication[d]	X					
Concomitant medication	X	X	X	X	X	X
Trial medication dispensing						
• trial patches[e]		X	X	X	X	
• metoclopramide	X	X	X	X	X	
• paracetamol		X	X	X	X	
Efficacy						
• Primary variable						
- Pain diary VAS, 2xdaily	X	X	X	X	X	X
• Secondary variables						
- Pain diary VAS, 4xdaily once a week	X		X	X	X	X
- Treatment assessment questionnaire (subject)					X	
- Global treatment assessment (investigator)					X	
• Quality of life: SF-36		X			X	X
• Functionality: WOMAC		X			X	X
Safety						
• Adverse events		X	X	X	X	X
• Vital signs	X	X			X[f]	X[f]
• SOWS						X
• Urine pregnancy test	X				X[g]	X[g]

[a] At the first visit, informed consent was obtained, demographic data and medical history were recorded and physical examination was performed
[b] early discontinuation visit (if applicable)
[c] Three days after the day the last patch was removed
[d] Previous medication included anti-inflammatory analgesics and/or weak opioids as well as possible other analgesic medication during the 2 weeks preceding the Run-In Period.
[e] On Days 4, 7 and 10 a phone call was made to check the need for a higher or lower dose of test medication.
[f] last visit or earlier if subject was withdrawn from the study
[g] During the last visit, i.e., V5 or V6 depending on last test medication dose

Statistical methods	Intent-to-treat analysis, t-test, ANOVA, Cochran-Mantel-Haenszel test, Van Elteren test, Wilcoxon's signed rank test, ANCOVA

[*] International Amendment III

Main features of the subject sample and summary of the results

Baseline characteristics - subject disposition Population: all subjects (AS)	**Placebo** N=200	**Durogesic** N=216
Subjects randomized (M/F; %)	32/68	35/65
Age: mean (SE), yrs	66 (0.7)	66 (0.7)
Age: median (min-max), yrs	67 (40-90)	66 (40-86)
Body weight: mean (SE), kg	82 (1.3)	81 (1.0)
Discontinuation of treatment – reason, n (%)		
• AE	20 (10)	62 (29)
• Insufficient efficacy	66 (33)	15 (7)
• Ineligible	0	1 (1)
• Lost to follow-up	0	2 (1)
• Non-compliant	3 (2)	3 (1)
• Consent withdrawn	13 (7)	21 (10)
• Other	4 (2)	6 (3)
Total	106 (53)	110 (51)

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Efficacy Population: ITT	**Placebo** N=197		**Durogesic** N=202		**p-value**[a]
	N		N		
Primary variable:					
• AAUCMB of VAS score[b] of pain severity (diary): mean (SE)[c]	197	-14.6 (1.4)	202	-20.0 (1.4)	0.007
Pain relief with Durogesic was superior to placebo in subjects with osteoarthritis of the knee or hip whose pain was inadequately controlled by weak opioids.					
• VAS scores, mean (SE):					
- Baseline[c]	197	73.3 (1.1)	202	73.1 (1.1)	0.976
- CFB at end point[c]	197	-17.9 (1.9)	202	-23.6 (1.8)	0.025
Secondary variables					
• AAUCMB (mean (SE)) for					
- Target joint pain right now[d]	180	-12.9 (1.4)	171	-18.7 (1.5)	0.002
- Average target joint pain today	196	-13.7 (1.6)	201	-20.0 (1.5)	0.002
- Global pain right now[c]	197	-12.0 (1.4)	202	-15.1 (1.4)	0.094
- Average global pain today	196	-10.6 (1.5)	200	-16.5 (1.5)	0.006
- Worst pain today	195	-12.5 (1.4)	201	-20.3 (1.5)	<0.001
- Pain impairing function today	195	-12.9 (1.5)	201	-17.8 (1.6)	0.011
- Current pain while walking today	195	-11.8 (1.5)	201	-19.8 (1.5)	<0.001
- Pain disturbing night rest	197	-12.0 (1.4)	202	-19.1 (1.7)	0.002
• Trial discontinuation: n (%)					
- For any reason	197	104 (53)	202	96 (48)	0.287
- Due to AE	197	20 (10)	202	54 (27)	<0.001
- Due to insufficient efficacy	197	64 (33)	202	15 (7)	<0.001
• Metoclopramide use:					
- At least once during Treatment Period: n (%)	197	74 (38)	202	126 (62)	<0.001
- Duration in % of Treatment Period (mean (SE))	197	27 (3.1)	202	41 (3.1)	

Efficacy (cont'd) Population: ITT	
• Treatment assessment questionnaire (answered by subject)	The treatment assessment questionnaire consisted of 10 items, scored by the subject on a 5-point Likert scale that differed for each item. Scores were summarized as favourable for the subject or unfavourable for the subject[e]. Most subjects of both treatment groups gave a favourable answer for items inquiring about ease of use. The number of subjects with a positive evaluation of side effects was statistically significantly lower in the Durogesic group than in the placebo group. Significant differences in favour of Durogesic were observed in terms of pain relief being similar to previous medication and whether the subject's overall expectations had been met.
• Global treatment assessment (by the investigator)	Investigators rated convenience of use as very good for both treatment groups according to the treatment assessment questionnaire. Scores for pain relief and overall impression were significantly better in the Durogesic group while the score for side effects was significantly better in the placebo group.
• Quality of life (SF-36)	The SF-36 showed moderate improvements in the physical items but little change in the mental health component. This may reflect the relatively short duration of treatment. Nevertheless, improvement of the physical health component scale relative to baseline was statistically significant in both treatment groups, indicating an overall improvement in physical health in parallel with pain relief. The bodily pain score was statistically significantly better in the Durogesic group than in the placebo group. Mean scores for the mental health component scale did not change significantly relative to baseline in either treatment group.
• Functionality (WOMAC)	Functionality, as represented by the overall WOMAC score and the pain, stiffness and physical functioning subscales, improved statistically significantly relative to baseline in both treatment groups. Improvement was moderately correlated with degree of pain relief as represented by VAS scores. The overall normalized WOMAC score and the normalized pain subscale were statistically significantly better for Durogesic subjects than for placebo subjects at end point. The normalized stiffness and physical functioning subscales also tended to be better in subjects receiving Durogesic, but the difference with placebo did not reach statistical significance.

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AAUCMB: average area under the curve minus baseline; CFB: change from baseline

[a] p-value for the difference between the treatment groups

[b] VAS score of 0-100 where 0= no pain and 100= worst possible pain

[c] for mean of morning and evening assessments

[d] for mean of weekly assessments (4 times daily)

[e] Definitions of favourable and unfavourable responses differed for each item: e.g. for item 1 ('How easy or difficult is it for you to use your trial patches?') the answers 'easy' and 'extremely easy' were regarded as favourable while 'neither easy nor difficult', 'difficult' and 'extremely difficult' were regarded as unfavourable.

Safety Population: AS	**Placebo** N=200	**Durogesic** N=216
Adverse events		
During entire period of drug exposure (Treatment Period and Tapering-Off Period):		
No. (%) with one or more AE	107 (54)	176 (82)
No. (%) of deaths	1 (1)	0
No. (%) with one or more serious AE	4 (2)	12 (6)
No. (%) treatment stopped due to AE	20 (10)	62 (29)
Most frequently reported AEs (≥ 5%):		
• Anorexia	0	10 (5)
• Constipation	3 (2)	22 (10)
• Diarrhoea	12 (6)	9 (4)
• Nausea	38 (19)	97 (45)
• Vomiting	5 (3)	64 (30)
• Insomnia	14 (7)	22 (10)
• Somnolence	8 (4)	48 (22)
• Yawning	4 (2)	11 (5)
• Fatigue	6 (3)	14 (7)
• Pain	13 (7)	12 (6)
• Sweating increased	2 (1)	16 (7)
• Temperature changed sensation	4 (2)	16 (7)
• Dizziness	11 (6)	27 (13)
• Headache	23 (12)	24 (11)
• Involuntary muscle contractions	6 (3)	14 (7)
• Pruritus	6 (3)	18 (8)
• Application site reaction	21 (11)	9 (4)
During Treatment Period:		
No. (%) with one or more AE	101 (51)	169 (78)
No. (%) of deaths	1 (1)	0
No. (%) with one or more serious AE	2 (1)	6 (3)
No. (%) treatment stopped due to AE	15 (8)	55 (26)
During Tapering-Off Period:[a]		
No. (%) with one or more AE	25 (14)	51 (28)
No. (%) of deaths	0	0
No. (%) with one or more serious AE	2 (1)	6 (3)
No. (%) treatment stopped due to AE	5 (3)	9 (5)
Nausea and vomiting in relation to metoclopramide use	During the Treatment Period, 113 Durogesic subjects (52%) and 40 placebo subjects (20%) reported at least one episode of nausea and/or vomiting. Of all subjects who reported nausea and/or vomiting in each treatment group, 96 (85%) Durogesic subjects used metoclopramide on at least one occasion, compared to 28 (70%) placebo subjects.	
Vital signs	No clinically relevant changes in vital signs were observed in subjects receiving either Durogesic or placebo.	
Withdrawal symptoms (SOWS)	Withdrawal symptoms were assessed using the SOWS questionnaire. The mean (SE) SOWS summary score was 0.66 (0.04) in the Durogesic group and 0.39 (0.02) in the placebo group ($p<0.001$).	

[a] Placebo: N=185; Durogesic: N=180

Conclusions

This trial demonstrates that Durogesic provided superior pain relief over placebo for patients with osteoarthritis of the knee or hip whose pain was inadequately controlled by weak opioids. Moreover, pain improved to a clinically relevant degree under Durogesic treatment and resulted in improved functionality and quality of life. The robustness of the result of the primary parameter was confirmed by the results of the secondary pain parameters, as well as the results of the subgroup analyses by target joint, baseline severity and use of concomitant analgesics.

The observed AE profile confirmed the known AE profile. Durogesic proved to be well-tolerated with minimal withdrawal symptoms during tapering-off.

Overall, the results of this trial indicate that Durogesic can provide a satisfactory pain relief for patients with moderate to severe pain.

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