SYNOPSIS

Trial identification and protocol summary

<table>
<tr><td colspan="2">Company : Janssen Research Foundation
Drug Name : Fentanyl
Drug No. : R04263
Trade Name: Durogesic</td></tr>
<tr><td>Title: A study to assess the safety, efficacy and pharmacokinetics of Durogesic in the treatment of paediatric subjects with chronic pain requiring long-term opioid therapy.</td><td>Trial No.: CR005950
Clinical phase: III</td></tr>
<tr><td>Investigator: AJ Goldman, MB, BChir, MRCP.
Other Investigators: Amery/Burne, Brady, Eden, Kohler, Latham, McDowell, Mitchell, Morland, Pearson, Phillips, Pinkerton, Walker.</td><td>Country: UK</td></tr>
<tr><td colspan="2">Reference: JRF Clinical Research Report CR005950, March, 2000</td></tr>
<tr><td>Trial period: Start: 01 February 1995
End: 30 September 1998</td><td>No. of investigators: 13
No. of subjects: 41</td></tr>
<tr><td colspan="2">Objectives:
To establish the analgesic efficacy, safety and pharmacokinetic profile of Durogesic in children in the treatment of chronic pain requiring long-term opioid therapy.
To provide health care professionals with experience of using Durogesic in the treatment of chronic pain requiring long-term opioid therapy.</td></tr>
<tr><td colspan="2">Trial design: This is an open study comprising three phases: a pre-trial phase, a Durogesic treatment phase and a follow-up phase.</td></tr>
<tr><td colspan="2">Patient selection:
• Inclusion criteria:
- Histologically, radiologically or haematologically confirmed malignancy, whose pain is judged by the investigator to be caused by the malignancy; or other life-threatening/terminal disease whose pain requires treatment with strong opioid analgesia.
- patients with pain requiring treatment with a strong opioid and who are expected to continue to require treatment with a strong opioid for the duration of the study. Subjects who are in the terminal stage of their disease and hence may not survive the course of the trial may still enter.
- current stable dose of immediate-release or sustained-release oral morphine for at least 48 hours immediately prior to entry into the trial. One or two additional doses of immediate-release morphine per 24-hour period in the pre-trial phase permitted for patents on sustained-release morphine. Minimum daily dose of 30 mg morphine.
- 18 years of age or younger upon study entry.
- Written informed consent, by patient or parents.
• Exclusion criteria:
- history of allergy or hypersensitivity to fentanyl or morphine.
- active skin disease that precludes application of Durogesic or that may affect the absorption of fentanyl or local tolerability.
- subjects whose clinical condition, in the investigator’s judgement, prevents participation in the study.
- Participation in any other drug trial relating to pain control within the last 1 month, or current inclusion in any other study or research project that could interfere with this trial.</td></tr>
</table>

Treatment:	
Form — dosing route	Patch —Transdermal
Medication	Durogesic (Fentanyl) supplied as 25, 50, 75 and 100-mcg/hr strengths
Batch number	Batch numbers are listed in Appendix 1.
Dosage	25–550 mcg/hr
Duration of treatment	15 days initially; long-term continuation allowed
Duration of trial	Treatment phase: 15 days; follow-up phase: as long as required by the subject. Maximum time in trial was 173 days.
Disallowed medication	Any opioid analgesia other than TTS-fentanyl and immediate-release morphine as described in the trial protocol.
Assessment:	
Efficacy	Primary efficacy parameter: Patient Treatment Assessment Secondary efficacy parameters: Pain level, use of rescue medication, constipation and diarrhoea record, play performance scale, investigator/parent global assessments and disease progression.
Safety	Adverse event incidence and severity were monitored as a safety parameter. Vital signs, skin site assessment and laboratory values were also monitored for safety.
Pharmacokinetics: Blood sampling	If possible 5 ml or — if unavoidable — 2.5 ml of venous blood was taken at various time points during the 15-day treatment interval.
Statistical methods	Binomial test, non-parametric sign test.

Main features of the patient sample and summary of the results

Baseline characteristics — patient disposition		
Number of subjects entered	41	
Age: median (min – max) years	10.5 (2.6–18. 8) years	
	Treatment Phase	**Follow-up Phase**
Reason for Discontinuation		
- Adverse experience	8	9
- Insufficient response	4	2
- Patient asymptomatic/cured	0	2
- Patient ineligible to continue in the trial	0	0
- Patient lost to follow-up	0	0
- Patient withdrew consent	3	3
- Patient non-compliant	0	0
- Other	0	3
TOTAL	15	19
Primary Efficacy: ***Treatment Phase***	**Success/N/% [95% CI]**	**p-value[#]**
Patient Treatment Assessment (Overall Patch Assessment)		
- Day 3 (success v non-success)	23/36/64% [48–80%]	
- Day 15^ (success v non-success)	27/36/ 75% [61–89%]	
- Comparison between Baseline v Day 15^	27/36	<0.001
Secondary Efficacy: ***Treatment Phase***	**Day 0[‡] N (%)**	**Day 15 N (%)**
Patient Treatment Assessment		
(1) pain controlled: well/not well	24/15 (61.5)	18/5 (72.0)
(2) drowsy: yes/no	23/16 (58.9)	12/12 (48.0)
(3) constipated: yes/no	25/14 (64.1)	13/11 (52.0)
(4) dry mouth: yes/no	23/15 (58.9)	8/16 (32.0)
(5) nausea/vomiting: yes/no	26/13 (66.6)	11/13 (44.0)
(6) itchy skin: yes/no	21/18 (53.8)	7/17 (28.0)
(7) sleeping well: yes/no	28/11 (71.7)	17/8 (68.0)
(8) medication convenient for patient: yes/no	22/15 (56.4)	22/2 (88.0)
(9) medication convenient for parent: yes/no	23/14 (58.9)	23/0 (92.0)
(10) usual activities continuing: yes/no	18/21 (46.1)	13/11 (52.0)
(11) wish to continue treatment post study: yes/no	32/1 (91.4) – Day 3	24/1 (96.0)
(12) Overall patch assessment		
- Very good	6	7
- Good	17	14
- Fair	9	4
- Poor	3	0
	Median (range)	
	Day 0	**Day 15**
Play Performance Scale	50 (10–100)	50 (0–100)

CI - Confidence interval
^ LOCF method
[‡] Day 3 for patient treatment assessment items 11&12
Based on the non-parametric sign test

Safety	**Day 0** **N**	**Treatment Phase** **N**	**Follow-up Phase** **N**
Adverse Events (AEs)			
Number of Events	20	138	104
Total Number of Subjects Assessed	41	41	23
Number with one or more AE	14	32	6
Number with one or more severe AE	6	23	14
Number with one or more serious AE	1	14	13
Number whose treatment stopped due to AE	0	10	7

	Median (range)	
	Day 0	**Day 15**
Vital Signs		
Pulse rate (beats/min)	100 (68–132)	100 (68–120)
Respiratory rate (breaths/min)	20 (14–40)	20 (16–32)

Disease Progression	**N (%)**
- Improved	1 (2.5%)
- No change	12 (30.0%)
- Slight deterioration	10 (25.0%)
- Marked deterioration	17 (42.5%)

Safety Comments:
A total of 262 adverse events (105 subjects) were reported from Day 0 to the end of the follow-up phase. The majority of these events were mild or moderate in severity. A total of 83 events were reported as severe: 9 on day 0 (6 subjects), 36 during the treatment phase (23 subjects) and 38 during the follow-up phase (14 subjects).

Relationship to study medication was reported as “possible” for 56/262 (21%) adverse events and as “definite” for 19/262 (7%) adverse events.

In total there were 39 serious adverse events (28 subjects). 2 SAEs (2 subjects) were reported on Day 0. 13 SAEs (12 subjects) were reported during the treatment phase, and 4 SAEs (4 subjects) occurred within 30 days of withdrawal/completion of the treatment phase. 15 SAEs (11 subjects) were reported during the follow-up phase, and 2 SAEs (2 subjects) were reported within 30 days of withdrawal/completion of the follow-up phase. 3 SAEs (3 subjects) occurred during the indefinite extension period. There were 25 patient deaths during the treatment and follow-up phases of the trial, including within 30 days of withdrawal/completion. All patient deaths were, in the opinion of the investigator, related to progression or complication of the patient’s underlying disease. None were considered related to the use of the study treatment. There were no apparent differences in the types or severity of adverse events reported during the treatment or follow-up phase.

None of the serious adverse events were considered by the investigator to be definitely related to the study medication. Five serious adverse events (3 subjects) were considered possibly related to the trial medication.

Pharmacokinetics:
Only a limited number of samples could be obtained in these subjects. Therefore no formal pharmacokinetic analysis could be performed.

Conclusions:
Durogesic appears to be an efficacious, convenient and well-tolerated method of pain control in children with chronic pain due to a life-threatening or terminal disease. The adverse event profile compares favourably with that of other opioid analgesics. Respiratory depression was not observed during this trial. A degree of caution should prevail in any inference from these trial results in view of the small number of subjects participating and actually completing this study. As there was no control group participating in this trial, it is difficult to distinguish effects due to treatment with the trial drug from effects due to methodology.

DISCLAIMER

Information in this posting shall not be considered to be a claim for any marketed product. Some information in this posting may differ from, or not be included in, the approved labeling for the product. Please refer to the full prescribing information for indications and proper use of the product.