SYNOPSIS

Trial Identification

Company: JANSSEN PHARMACEUTICA N.V. **Finished Product**: Duragesic®/Durogesic **Active Ingredient**: Fentanyl	
Title: A 15-day trial to document the safety, clinical utility and pharmacokinetics of Duragesic® (TTS fentanyl) in the treatment of pediatric subjects with continuous pain requiring opioid therapy.	**Trial No.**: CR005962 **Clinical phase**: III
Investigator: Multicenter	**Country**: Europe
EDMS-PSDB-1283222	
Reference: None	
Trial period: Start: 02 June 1999 End: ongoing	**No. of investigators**: 13 **No. of subjects enrolled**: 53 **No. of subjects dosed**: 53

Protocol Summary

Indication / Objectives: Continuous pain / to determine the safety, clinical utility, and pharmacokinetics of 12.5 µg/h Duragesic in the treatment of subjects aged 2-12 years with continuous pain requiring the use of a potent opioid.
Trial Design: Single arm, non-randomized, open-label, multicenter trial with a 15-day primary treatment period followed by a long-term treatment extension period of up to 1 year.
Main Selection Criteria: Subjects who participated in the study were: i) between 2-12 years of age (extremes included); ii) suffered from continuous pain of a well documented etiology; and iii) had pain that required treatment with a strong opioid. Subjects who were experiencing pain from mucositis, and in the investigator's opinion were expected to require treatment with a strong opioid for at least 7 days, were considered for the study. Reasons subjects could be excluded from the study included: i) a history of allergy or hypersensitivity to fentanyl or morphine; ii) active skin disease that precluded application of Duragesic or which may have affected the absorption of fentanyl or local tolerability (this did not necessarily exclude lesions which could be avoided); or iii) life expectancy that was less than 1 month.

Treatment					
Form - dosing route	Transdermal patch applied to nonirritated and nonirradiated skin on a flat surface of the upper torso.				
Medication	12.5 µg/h Patch	25 µg/h Patch	50 µg/h Patch	75 µg/h Patch	100 µg/h Patch
Batch number	9801242 9907880	0001202 0009804 0001202 0009804	9910754 0009541	9915113 201350	0001203
Dosage	The initial dose of Duragesic for all subjects was 12.5 µg/h (1 patch). The patches were to be replaced every 72 hours. An increased dose may have been used when a higher dose was needed based on rescue medication consumption and pain assessment.				
Duration of treatment	15 days with up to 1 year in the treatment extension period.				
Duration of trial	15 days with up to 1 year in the treatment extension period.				
Disallowed medication	All opioid analgesics except Duragesic and morphine. If anesthesia was performed, care was taken not to use fentanyl.				

Statistical Methods:

The analyses presented in this report are based on a closed database consisting of all primary treatment period data from all subjects enrolled in the study and any extension data that were received for the database by 23 March 2001.

Subject disposition and demographics and baseline characteristics were summarized descriptively. All safety and efficacy/clinical utility data were summarized for the Intent-to-Treat population (ITT), defined as all enrolled subjects regardless of compliance, unless no Duragesic medication was taken. The efficacy/clinical utility parameters (treatment assessment, global assessment, pain levels, and play performance) were summarized descriptively by timepoint for the primary treatment period only, overall and by sex and age category. The Play Performance Scale scores were also examined in the context of changes with other clinical utility parameters which included treatment assessment, pain as reported by the child and investigator, average daily dose, and dosing and titration information. Dosing and titration information was summarized descriptively for the primary treatment period, extension period, and both periods combined, overall and by age category, body weight category, and for opioid-naive and opioid-exposed subjects. Rescue medications were summarized separately for the primary treatment period and the extension period, overall and by age category, body weight category, and for opioid-naive and opioid-exposed subjects.

Adverse event (AE) incidence summaries included: overall, by severity, by relationship, those defined to be related to trial medication, serious adverse events (SAEs), and adverse events leading to withdrawal. All these summaries were presented for all subjects in the Intent-to-Treat population as well as by the subgroups: age category, body weight category, opioid-naive and opioid-exposed category, and the Tanner Sexual Maturity Rating Scale. Overall adverse events and adverse events defined to be related to trial medication were also summarized separately for the primary treatment period and extension period, overall and by the same subgroups. Physical examination results and vital signs were summarized descriptively.

All data obtained and recorded for the primary treatment period and any available extension data for this report are presented in subject data listings for the Intent-to-Treat population, including protocol deviations, deaths, serious adverse events, and adverse events leading to withdrawal.

Main features of the subject sample and summary of the results

Baseline Characteristics - Subject Disposition

A total of 53 subjects were enrolled in the study and included in the Intent-to-Treat population. Twenty-eight of these subjects were male and 25 were female. Mean age was 6.5±0.47 years. Twenty-nine subjects (54.7%) were in the 2-6-year age group and 24 subjects (45.3%) were in the 7-12-year age group. Over 80% of subjects had prior opioid exposure. A total of 27 subjects withdrew from the study during either the primary or extension treatment periods. Reasons for withdrawal included death (11 subjects, 20.8%: note that 10 subjects died during the trial and 1 after withdrawal), insufficient response (4 subjects, 7.5%), adverse events (3 subjects, 5.7%), subject ineligible to continue the trial (3 subjects, 5.7%), withdrawn consent (1 subject, 1.9%), and other reasons (5 subjects, 9.4%). (Of note, 1 of the 11 subjects who died did so after withdrawing from the study.)

Pharmacokinetic Results

The dose-normalized serum fentanyl concentrations did not show any apparent trends across measures at 72 hours post each dose for a 5 patch (dose) treatment over 15 days, suggesting no apparent accumulation of fentanyl occurred during chronic treatment. The serum concentration of fentanyl reached steady state at 24 hours post first patch. Approximate dose proportionality was observed for fentanyl from 12.5 to 37.5 μg/h; no assessment could be made for doses of 50 μg/h, 62.5 μg/h, 100 μg/h, and 150 μg/h due to insufficient data.

Efficacy/Clinical Utility

For subjects who had a treatment assessment of fair or poor regarding their current pain therapy at baseline, the majority (64.3%) improved to an assessment of good or very good at endpoint for the treatment of Duragesic patch, whereas 35.7% remained as fair or poor. For subjects who had a treatment assessment of good or very good regarding their current pain therapy at baseline, the majority (92.9%) remained so at endpoint for the treatment of Duragesic patch, whereas 7.1% worsened to an assessment of fair or poor. Most of the subjects who had an investigator's global assessment of pain treatment (pain control) at endpoint had an assessment of excellent or good (73.3%). A majority of subjects (73.6%) had a pain intensity assessed by the investigator of moderate, severe, or very severe at baseline. In contrast, most of subjects (71.7%) had an assessment of none or mild at endpoint. Average daily pain intensity levels assessed by the subject decreased steadily over time for both the Bieri Faces Scale and the Varni Thompson Visual Analogue Scale. Overall, 86.8% of subjects took at least 1 rescue medication during the primary treatment period, with average oral morphine-equivalent dose of 12.2±1.65 mg. Overall, an improvement in the subject's functioning based on the final Play Performance Scale scores was observed. Improvements were associated with the reduction of pain intensity as assessed by the subject and investigator and with the subject's positive assessment of treatment in terms of convenience, pain control and side effects. Most of subjects (67.9%) never required an upward titration of Duragesic above the initial dose during the primary treatment period. The average daily Duragesic dose was 16.9±1.25 μg/h during the primary treatment period.

Safety	Duragesic (ITT Population: N=53)
No. (%) of deaths[1]	10 (18.8%)
No. (%) with 1 or more serious adverse events[2]	18 (34.0%)
No. (%) treatment stopped due to adverse events	3 (5.7%)
No. (%) with 1 or more adverse events	45 (84.9%)
Most frequently reported treatment-emergent adverse events (≥10%):	
• Fever	18 (34.0%)
• Anemia	15 (28.3%)
• Nausea	13 (24.5%)
• Vomiting	11 (20.8%)
• Thrombocytopenia	11 (20.8%)
• Constipation	9 (17.0%)
• Pain	8 (15.1%)
• Pruritus	8 (15.1%)
• Neuroblastoma[3]	6 (11.3%)
• Somnolence	6 (11.3%)

[1]Includes treatment-emergent deaths only. An additional subject died after withdrawing from the study (Subject A30123).

[2]Includes treatment-emergent SAEs only. An additional subject had an SAE after withdrawing from the study (Subject A30123).

[3]For this study disease progression is an adverse event.

As shown in the table above, 10 subjects (18.8%) died during this study and 1 subject died after withdrawing from the study (acute leukemia). None of the deaths were considered by the investigator to be related to treatment with Duragesic. Serious adverse events were reported for 18 subjects (34.0%) during the study. An additional subject had a serious adverse event (acute leukemia) after withdrawing from the study. Two subjects had serious adverse events that were considered by the investigator to be related to treatment with Duragesic (hyperesthesia and pain; stupor, miosis, somnolence, and respiratory disorder). One of these subjects withdrew from the study as a result of the serious adverse events (hyperesthesia and pain). None of the events reported as serious adverse events raised any unexpected safety concerns.

The incidence of subjects who withdrew from the study due to an adverse event was low (3 subjects, 5.7%). All 3 subjects withdrew during the primary treatment period. One subject withdrew due to the serious adverse events of hyperesthesia and pain of hands and feet. The second subject withdrew due to adverse events that included fatigue, speech disorder, and abnormal thinking and the third subject withdrew due to constipation. All of these events were considered by the investigator to be related to trial medication.

The incidence of subjects who had an adverse event that required a dose adjustment was also low (3 subjects, 5.7%). One subject required a dose decrease (from 25 μg/h to 12.5 μg/h) as a result of vomiting (adverse event). There were no subjects in this study who required a temporary stop in trial medication due to an adverse event.

The majority of subjects (84.9%) reported at least 1 adverse event during treatment. The most common adverse events included fever, anemia, nausea, vomiting, and thrombocytopenia.

About 50% of the subjects in the Intent-to-Treat population reported at least 1 severe adverse event. The most common severe adverse events were neuroblastoma, pain, somnolence, and nausea.

Most subjects (58.5%) had adverse events that were considered by the investigator as not related to trial medication. The most common related events were constipation, nausea, somnolence and pruritus.

The incidence of individual adverse events that may be associated with respiratory depression (respiratory depression, respiratory disorder, apnea, and hypoxia) was ≤4% and the majority of these events were considered by the investigator to be not related to trial medication. The incidence of the adverse events commonly associated with the use of an opioid analgesic (nausea, vomiting, and constipation) was ≤25%. In addition, 2 subjects reported an application site adverse reaction during the study.

Results of subgroup analysis showed that there were some notable differences in the safety profiles within the different subgroups. In general, the incidence of adverse events was higher among subjects in the 2 to 6 year age group, in the opioid-exposed group, and in subjects who were in the first and second-third quartiles for weight. This includes serious adverse events, severe adverse events, and events considered related to study drug. However, the overall incidence of adverse events and the incidence of related adverse events in the opioid-naive and opioid-exposed groups was similar. With regard to the most common adverse events, there were some differences in overall incidence within the subgroups but none were clinically meaningful.

Forty-five of 53 subjects (84.9%) who entered the primary treatment period had at least 1 adverse event during this period. All 10 subjects (100%) in the extension period experienced at least 1 adverse event during the extension period. No adverse events were observed during the extension treatment period that would represent a safety concern. In both treatment periods, the majority of subjects had adverse events that were considered by the investigator as not related to trial medication.

An evaluation of vital sign and physical examination data did not raise any safety concerns.

Conclusions

Duragesic appears safe and well tolerated over a large dose range (12.5-150 µg/h for a 2-week treatment period) in children with continuous pain requiring opioid therapy. The Duragesic safety profile in the pediatric population did not show unexpected or new side effects not seen in the adult population.[1] Respiratory depression was not a concern when Duragesic was used appropriately. There were no deaths considered by the investigators to be related to the treatment and the incidence of withdrawal in the primary period due to adverse events was low (5.7%).

Serum fentanyl concentrations showed intersubject variability and dose proportionality for the 12.5 to 37.5 µg/h dosages. No assessment could be made for dose of 50, 62.5, and 100 µg/h due to insufficient data. Steady state was reached at 24 hours post first-patch application and stayed stable over time.

Although the study focused on safety and did not have a defined primary efficacy parameter, the clinical utility endpoints (treatment assessment, global assessment, pain intensity, play performance) and dosing titration provided positive information on the therapeutic benefit of Duragesic in children suffering from chronic pain who required opioid treatment.

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