SYNOPSIS

Name of Sponsor/Company:	Janssen Medical Affairs, L.L.C.	
Name of Finished Product:	Duragesic® (fentanyl transdermal system)	
Name of Active Ingredient(s):	Fentanyl	

Protocol No.: CR002446

Title of Study: Assessing functionality changes associated with patients who were taking short acting opioids chronically and who initiated treatment with Duragesic® for the management of chronic low back pain.

Investigator: Multi-center study

Publication (Reference): Kosinski MR, Schein JR, Vallow SM, et al. An observational study of health-related quality of life and pain outcomes in chronic low back pain patients treated with fentanyl transdermal system. Curr Med Res Opin 2005;21:849-862.

Study Period: 23 July 2002 to 06 Jan 2004 | **Phase of development:** 4

Objectives: To assess changes over a minimum period of 9 weeks in functionality using the Oswestry Disability Index in patients with chronic low-back pain who are taking short acting opioids chronically and who initiate concomitant treatment with Duragesic® (fentanyl transdermal system).

Methodology: This was a usual-care, naturalistic, observational, open-label, prospective trial. Pain clinic outpatients with chronic, non-cancer related low back pain who had been taking short-acting opioids were initiated on Duragesic® (fentanyl transdermal system) treatment according to usual care practice. Patients were followed for a minimum of 9 weeks to determine whether initiating Duragesic® (fentanyl transdermal system) treatment had any effects on disability, functionality and health-related quality of life. The primary analyses were performed on the efficacy-evaluable population. This was defined as patients who were treated during the course of the trial, had two measurements on the primary outcome measure (pre-treatment and follow-up), the Oswestry Disability Index (ODI), with the second measurement being at least 9 weeks after the baseline measurement, and were not on other long-acting opioids (LAOs) at either baseline or during the course of the trial.

Number of Subjects (planned and analyzed): 358 patients entered the study and 131 were evaluated for efficacy.

Diagnosis and Main Criteria for Inclusion: Patients with chronic, non-cancer related low back pain who were taking short-acting opioids for at least 4 weeks and initiating Duragesic® (fentanyl transdermal system).

Test Product, Dose and Mode of Administration, Batch No.: Duragesic® (fentanyl transdermal system) administered according to usual practice of the physician.

Batch number: Not applicable

Reference Therapy, Dose and Mode of Administration, Batch No.: Not applicable

Duration of Treatment: At least 9 weeks.

Criteria for Evaluation:

Efficacy: The primary efficacy variable was the Oswestry Disability Index (ODI). The secondary efficacy variable was the Total Pain Experience Scale (TPE) of the Treatment Outcome in Pain Survey (TOPS). The Numeric Rating Scale (NRS) of Pain, other TOPS subscales and the Work Productivity and Activity Impairment Questionnaire comprised the tertiary efficacy variables.

Safety: Adverse events were recorded, and their type and incidence were tabulated.

Statistical Methods: The primary null hypothesis of the trial was that there is no difference in the ODI score from baseline to follow-up for all patients. The secondary null hypothesis was that there is no difference in the Total Pain Experience subscale of the TOPS from baseline to follow-up for all patients. The tertiary null hypotheses were that there are no differences from baseline to follow-up in the NRS, the remaining 15 TOPS subscales, or in work status and hours worked and productivity while at work. In addition, another tertiary null hypothesis was that the mean OTE score does not statistically significantly differ from 0. Change was assessed via paired t-test comparison of baseline to endpoint score on the ODI and TOPS. No adjustments for multiplicity were made for secondary and tertiary comparisons as they were exploratory. In addition, several multivariate models were developed to aid in the explanation of significant findings of the primary and secondary endpoints. An overall significance level of 0.05 (two-sided) was used for interpretation of statistical significance.

SYNOPSIS (CONTINUED)

SUMMARY - CONCLUSIONS

Of the 358 patients enrolled in the study, 251 were completers. Of these, 181 patients completed their follow-up ODI after 9 or more weeks of treatment. Of these 181 patients, 24 terminated prematurely. An additional 26 were excluded because of protocol violations. Consequently, the efficacy evaluable population comprised 131 patients (mean age 46.2 years), 49 of whom were males.

EFFICACY RESULTS:

There was a significant improvement in the ODI over the course of the trial (7.1 points, $p<0.0001$; 95% CI=4.7, 9.5). The magnitude of improvement was greater than the estimates of minimal important differences (MIDs) obtained from the study (estimated to be in the 5.5-6.6 range) or found in the literature and used in powering the study. There was also significant improvement on the secondary endpoint, the Total Pain Experience Subscale (TPE) of the Treatment Outcomes in Pain Survey (TOPS) (7.8 points, $p<0.0001$; 95% CI=5.8, 9.8), which was also greater than the MID estimated from the data in the study (estimated to be in the range of 3.9-6.5). Among the tertiary endpoints, there was significant improvement in the Numeric Rating Scale of pain (1.5 points, $p<0.0001$; 95% CI=1.2, 1.9), as well as on the following TOPS scales: Pain Symptoms, Lower Body Functional Limitations, Upper Body Functional Limitations, Perceived Family/Social Disability, Life Control, Work Limitations, Patient Satisfaction with Outcomes, Health Care Satisfaction, and the Vitality and the Mental Health Scales from the SF-36 portion of the TOPS. Each of the following TOPS scales improved from baseline to the end of the trial, but did not reach statistical significance: Objective Family/Social Disability, Objective Work Disability, Passive Coping, and Solicitous Responses.

Multivariate models were used to help explore predictors for ODI and TPE scores, with predictors grouped into clinical variables (e.g., duration of back pain), psychiatric variables (e.g., depression status), or treatment variables (e.g., use of physical therapy). The improvement in pain and, to a lesser extent, the number of concomitant pain conditions at baseline were the only variables that consistently predicted improvement in ODI or TPE in the models. Hence, the data support the conclusion that patient functionality improved because of the positive impact of Duragesic® (fentanyl transdermal system) on patient pain

SAFETY RESULTS:

There were 43 AE preferred terms; 106 patients experienced 146 AEs. Thirty eight (26.0%) were rated as mild; 65 (44.5%) were rated as moderate; and 42 (28.8%) were rated as severe. Skin irritation (9%), nausea (6%) and vomiting NOS (6%) were the most frequently reported AEs. Twenty six (17.8%) AEs were not related to study drug; 2 (1.4%) were rated as doubtful; 13 (8.9%) were rated as possible; 25 (17.1%) were rated as probable; and 79 (54.1%) were rated as very likely related to study drug. An AE of nausea was reported with unknown severity and unknown relation to study drug. Four patients experienced 5 serious adverse events, only one of which was deemed to be drug related; there were no deaths.

CONCLUSION:

In this study, it was not possible to rule out whether various treatments interacted in a non-linear fashion to account for the improvements in patients. Given the usual care aspect of the study, prescription to Duragesic® (fentanyl transdermal system) was not the only action that patients were permitted to take to treat their CLBP; physical therapy, used of short acting opioids, exercise, etc. were all permitted to occur during the study. The study is also limited by the lack of a control group and randomization.

Notwithstanding the above limitations, this usual care study demonstrates that subjects who were taking short acting opioids chronically and who initiated treatment with Duragesic® (fentanyl transdermal system) as part of their physician's normal treatment pattern showed improvement in several areas, including disability (assessed by the ODI), health-related quality of life and functionality (assessed by the TOPS), and pain (assessed by the NRS) over the course of this naturalistic trial.

Date of the report: 9/28/04

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