2. SYNOPSIS

<table>
<tr><td>Name of Company:
Mundipharma Research GmbH & Co. KG</td><td>INDIVIDUAL STUDY TABLE</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Name of Finished Product:
Oxycodone/naloxone prolonged-release tablets (OXN)</td><td rowspan="2">Referring to Part IV of the Dossier

Volume: Page:</td></tr>
<tr><td>Name of Active Ingredient:
Oxycodone/naloxone combination</td></tr>
<tr><td colspan="3">Title of the Study: An Open-label Study to Determine the Long-term Safety and Efficacy of Oxycodone/Naloxone Prolonged-release Tablets in Subjects with Moderate to Severe, Chronic Nonmalignant Pain</td></tr>
<tr><td colspan="3">Investigator(s)/Center(s):
Sites:
Austria: 6 sites Germany: 43 sites Spain: 11 sites
Czech Republic: 18 sites Hungary: 10 sites
Denmark: 3 sites Slovakia: 9 sites</td></tr>
<tr><td colspan="3">Publication (Reference): None</td></tr>
<tr><td>Study Dates:
17 May 2005 to 27 Apr 2007</td><td>Study Status:
Completed</td><td>Phase of Development:
Phase 3</td></tr>
<tr><td colspan="3">Objectives: The objective was to assess the long-term efficacy and safety of oxycodone/naloxone.</td></tr>
<tr><td colspan="3">Methodology: This was an uncontrolled, open-label, longitudinal study using oxycodone/naloxone (OXN) to treat moderate to severe, chronic nonmalignant pain.</td></tr>
<tr><td colspan="3">Number of Subjects: Planned: 450 subjects. Completed Core (Double-Blind) Phase: 402 subjects (133 received OXY, 136 received OXN, 133 received placebo). Extension Phase: 380 subjects entered the Extension Phase, 379 subjects received study medication, 296 subjects completed the Extension Phase.</td></tr>
<tr><td colspan="3">Indication and Criteria for Inclusion: Males and females 18 years of age or older with documented history of moderate to severe chronic low back pain that required around-the-clock opioid therapy. Subjects had completed the Double-blind Phase, required continuation of daily opioid analgesic treatment, and were likely to benefit from chronic opioid therapy for the duration of the Extension Phase.</td></tr>
<tr><td colspan="3">Test Treatment, Dose, and Mode of Administration:
Extension Phase: OXN 10/5, 20/10, and 40/20 mg oxycodone/naloxone combination tablets</td></tr>
<tr><td colspan="3">Reference Treatment, Dose, and Mode of Administration:
none</td></tr>
<tr><td colspan="3">Duration of Treatment: up to 52 weeks.</td></tr>
<tr><td colspan="3">Treatment Schedule: At Visit 8b, subjects meeting the Extension Phase Entrance Criteria (ie, completed the Double-blind Phase) had the option to receive open-label oxycodone/naloxone for up to 12 additional months during the Extension Phase. All subjects were switched to 20/10 mg/day oxycodone/naloxone. Dose titration was permitted up to 80/40 mg/day at the discretion of the investigator.</td></tr>
<tr><td colspan="3">Criteria for Evaluation:</td></tr>
</table>

Analysis Populations: Extension population: The subset of the double-blind safety population that was exposed to oxycodone/naloxone during the Extension Phase; Subgroup population: Subpopulation of the extension population with oxycodone/naloxone PR doses of >40/20 mg per day on more than 7 consecutive days.

Efficacy: modified Brief Pain Inventory- Short Form (modified BPI-SF), change in the dose from the randomised dose to the end of the Extension Phase, as well as after two weeks of the Extension Phase.

Safety: Safety was monitored by collecting the following data: adverse events, vital signs, clinical laboratory results and electrocardiograms (ECGs).

Statistical Methods:

Efficacy Analyses:

There was no primary efficacy variable / endpoint the study was powered for.

Modified BPI-SF: all 12 single items were analysed by descriptive statistics only. Summary statistics were provided for the average pain over 24 hours, the pain subscale, the sleep interference and the interference subscale.

For dose changes during the study period a shift table with numbers of changes from the dose at the start of the Double-blind Phase to the oxycodone/naloxone dose at the end of the Extension Phase as well as the oxycodone/naloxone dose after two weeks of the Extension Phase was provided. Changes after two weeks of the Extension Phase were displayed by treatment group of the Double-blind Phase.

Safety Analyses: The incidence of adverse events was tabulated. Clinical laboratory results, vital signs, and ECG findings were summarised.

Results:

Efficacy: Mean 24 hour pain scale values and BPI-SF pain subscores were low and stable over 6 and 12 months and comparable to the end of core study values, which indicated a good analgesic efficacy during long-term treatment with oxycodone/naloxone. These results were supported by the BPI-SF sleep quality item and interference subscores which correlated very well with the low pain scale values and indicated a positive effect on interference of pain with sleep and activities, which was maintained throughout the Extension Phase. For the subgroup of subjects receiving higher doses than 40/20 mg oxycodone/naloxone PR per day on more than 7 consecutive days, the mean average pain during the last 24 hours (SD) was stable and comparable at all visits throughout the extension phase, indicating that oxycodone/naloxone PR is an effective analgesic drug in this subgroup population. After the first two weeks of the Extension Phase, the majority of subjects remained on an oxycodone/naloxone dose that was comparable to their treatment during the Double-blind Phase. The percentage of subjects with a dose increase or a dose decrease was comparable and independent from the different treatment groups from which subjects were switched to oxycodone/naloxone. There was no indication that the treatment they were assigned to in the Double-blind Phase had an influence on the dose increase after the first 2 weeks. At the end of the Extension Phase the majority of subjects remained on a stable oxycodone/naloxone dose or had a slight dose decrease or increase. Uptitration was allowed as it was expected due to the natural progression of the underlying chronic pain condition over the 12-month time period. Throughout the Extension Phase the mean total daily dose increased from 29.5 mg to 43.7 mg indicating a natural progression of the underlying chronic pain condition over this long time period. Furthermore it has to be considered that the intake of rescue opioid medication was very low, which could represent an additional factor for the increase in the study medication dose.

Safety: There were no significant changes in clinical laboratory tests, vital signs and ECGs during the study. The incidence of adverse events during the Extension Phase (68%) was comparable to the Core Phase (oxycodone/naloxone 55.8%, oxycodone 53.0%, placebo 52.5%), taking into consideration the longer observation period of 12 months, compared to 3 months in the Core Phase. Only 38% of the subjects experienced related AEs. 6.3% of the subjects experienced AEs that led to discontinuation. Constipation (n=35; 9.2%), nausea (n=29; 7.7%), back pain (n=24; 6.3%) and depression (n=24; 6.3%) were the most frequently reported adverse events. Constipation and nausea are common side-effects of treatment with a strong opioid, whereas back pain and depression may be correlated to the underlying medical condition. The incidence of constipation was highest in the first 3 months of the Extension Phase (n=13; 3.4%). In this sensitive phase, all subjects restarted opioid treatment with 20 mg oxycodone/naloxone, were uptitrated to their effective analgesic dose and started new analgesic co-medication. Throughout the next 9 months, the incidence of constipation consistently decreased, dropping from 6 subjects at 3 to 6 months to one subject at greater than 12 months. The incidence of constipation increased again to 12 subjects within 7 days after the end of oxycodone/naloxone treatment and the switch to a marketed product. In 11 subjects, constipation was assessed by the investigator as not related to study medication (2.9%). Therefore, the incidence of constipation related to study medication is reduced to 6.3%. The incidence (3.2%) and mean duration (6 days) of diarrhoea were generally low. Three subjects experienced diarrhoea during the first two weeks of the Extension Phase. All three subjects received a total daily dose of 40 mg oxycodone during the Core Phase and restarted treatment during the Extension Phase with 20/10 mg oxycodone/naloxone per day. In this sensitive phase all subjects were uptitrated to their effective analgesic dose. The lower dose at the start of the Extension Phase could have been a factor impacting on the bowel function causing diarrheal symptoms, which disappeared after a few days of treatment with oxycodone/naloxone. 48 subjects (13%) experienced 88 SAEs during the Extension Phase. 12 subjects (3.2%) experienced 27 SAEs that were rated by the investigators as having a positive causal relationship to study drug. 6 SAEs in only 3 subjects were assessed as being possibly related to study drug by the investigator and 2 additional SAE in 2 subjects were assessed as being possibly related to study drug by the sponsor. Due to the low number of subjects that experienced SAEs, which were at least possibly related, oxycodone/naloxone showed no additional risk compared to other opioid treatments. One subject died during the Extension Phase due to a quadricycle accident. The investigator found the adverse event not to be related to treatment with study medication. Two subjects reported an adverse event related to opioid withdrawal, which started after the end of study medication intake and were therefore probably related to the change of opioid treatment. The incidence of adverse events leading to discontinuation during the Extension Phase was very low (n=24). The AE, which most frequently led to discontinuation was nausea (n = 3). Data do not imply an increased safety risk to subjects taking doses above 40/20mg/day oxycodone/naloxone PR for more than 7 consecutive days, compared to the total extension population. There was no indication of a medically relevant increase in the nature, frequency, or intensity of adverse events or suspected adverse drug reactions in the higher dose subgroup.

Conclusions: This study provides supportive evidence for the long-term efficacy and safety of oxycodone/naloxone. In the dose range investigated the addition of naloxone to oxycodone in a prolonged release combination tablet has no negative effect on the pain relief of subjects. After the first two weeks of the Extension Phase, the majority of subjects remained on an oxycodone/naloxone dose that was comparable to their treatment during the Double-blind Phase. There was no indication that the treatment subjects were assigned to in the Double-blind Phase had an influence on the dose increase after the first 2 weeks. At the end of the Extension Phase the majority of subjects remained on a stable oxycodone/naloxone dose or had a slight dose decrease or increase. Uptitration was allowed as it was expected due to the natural progression of the underlying chronic pain condition over the 12-month time period. Throughout the Extension Phase the mean total daily dose increased from 29.5 mg to 43.7 mg indicating a natural progression of the underlying chronic pain condition over this long time period. Furthermore it has to be considered that the intake of rescue opioid medication was very low, which could represent an additional factor for the increase in the study medication dose. No apparent safety concerns of treatment with oxycodone/naloxone were identified. Importantly, adverse events were not exacerbated by the addition of naloxone to oxycodone therapy. Due to the low number of subjects that experienced SAEs, that were at least possibly related, oxycodone/naloxone showed no additional risk compared to other opioid treatments. A subgroup analysis do not imply an increased safety risk to subjects taking doses above 40/20mg/day oxycodone/naloxone PR on more than 7 consecutive days, compared to the total extension population. There was no indication of a medically relevant increase in the nature, frequency, or intensity of adverse events or suspected adverse drug reactions in the higher dose subgroup. The mean average pain during the last 24 hours (SD) was stable and comparable at all visits throughout the extension phase, indicating that oxycodone/naloxone PR is an effective analgesic drug in this subgroup population.

Date of the Report: 10-Oct-2007