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 PR 5/2.5 mg, 10/5 mg, 20/10 mg, 40/20 mg)</td><td rowspan="2">Referring to Part … of the Dossier

Volume: Page:</td></tr>
<tr><td>Name of Active Ingredient:
oxycodone/naloxone</td></tr>
<tr><td colspan="3">Title of the Study: A randomised, double-blind, double-dummy, parallel-group multicentre study to demonstrate non-inferiority in pain and locomotor function and improvement in symptoms of constipation in subjects with moderate to severe pain due to osteoarthritis (OA) of the knee and/or hip taking oxycodone equivalent of 20 - 80 mg/day as oxycodone/naloxone prolonged release (OXN PR) compared to subjects taking oxycodone prolonged release tablets (OxyPR) alone.</td></tr>
<tr><td colspan="3">Investigator(s): 81 sites in Switzerland (1), The Netherlands (4), Austria (3), Belgium (5), Czech Republic (18), Finland (2), Germany (16), Hungary (9), Israel (4), Poland (11) and Spain (8).</td></tr>
<tr><td colspan="3">Publication (Reference): None.</td></tr>
<tr><td>Study Dates:
06 May 2009 to 02 August 2010</td><td>Study Status:
Completed</td><td>Phase of Development:
Phase 3</td></tr>
<tr><td colspan="3">Objectives: The primary objectives were:
• to demonstrate that the treatment with OXN PR tablets is non-inferior to the treatment with OxyPR with regards to analgesic efficacy and locomotor function as assessed by the Western Ontario and McMaster Universities Osteoarthritis Composite Index (WOMAC VA3.1, visual analogue scale) in subjects with moderate to severe OA pain.
• to demonstrate that subjects with moderate to severe OA pain taking oxycodone/naloxone prolonged release tablets have improvement in symptoms of constipation as measured by the bowel function index (BFI) compared to subjects taking oxycodone prolonged release tablets alone.

The secondary objectives were:
• to estimate the subjects' average pain over the last 24 hours assessed at each double-blind study visit during treatment with OXN PR compared with OxyPR.
• to assess subject assessment of opioid-induced constipation, constipation symptom severity, impact and bothersomeness based on the PAC-SYM(b).

Exploratory efficacy objectives included assessment of Complete Spontaneous Bowel Movements (CSBMs), frequency of laxative use, Modified Brief Pain Inventory Short-Form (BPI-SF), rescue medication use and the SF-36 v2 health survey.</td></tr>
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Methodology:
Pre-randomisation Phase (up to 42 days):
Screening (up to 14 days): At Visit 1, after written informed consent was obtained, subjects underwent complete evaluation for study eligibility (i.e., all inclusion/exclusion criteria). Subjects meeting the Prospective Assessment Criteria continued in the study.
Run-in (7 to 28 days): At Visit 2, subjects had their opioid therapy converted to open-label oxycodone prolonged release (OxyPR), which was titrated to an effective analgesic dose between 20 - 80 mg/day of OxyPR (20, 30, 40, 50, 60, 70 and 80 mg/d). Oxycodone immediate release (OxyIR) was available as rescue medication. Subjects also had their pre-study laxative therapy converted to the study laxative to be used per the study routine for constipation during this period, no sooner than 72 hours after their most recent bowel movement (BM) as rescue medication for constipation. However, investigators instructed their subjects that if they exhibited discomfort during the 72 hour period they could take oral bisacodyl as a laxative earlier than 72 hours after their most recent bowel movement as required to treat constipation. The maximum allowed number of bisacodyl intakes was 5 dosages bisacodyl 10mg/day within the last 7 days of the Run-in Period. The 7-day baseline assessment in the Run-in Period started no sooner than the day of the initial dose conversion to OxyPR.

Double-blind Phase (12 weeks):
At Visit 3, subjects who qualified for entry into the Double-blind Phase of the study were randomised to OXN PR or OxyPR in a 1:1 ratio. Subjects received double-blind study medication for up to 12 weeks. The switch to the study medication was done in a stepwise manner over a period of 4 days regarding the naloxone dose within the first week of Double-blind Phase for the 60, 70 and 80 mg oxycodone PR/day doses. For subjects on the 20-50 mg oxycodone PR/day doses the study medication was switched directly. During the Double-blind Phase the subjects continued to use study laxatives as described above. Subjects were asked not to take any laxative for the first 3 days after the randomisation visit (V3). However, investigators instructed their subjects that if they exhibited discomfort during this period they could take oral bisacodyl as a laxative earlier, as required to treat constipation. OxyIR was prescribed as rescue medication up to 6 times a day at a dose of approximately 1/6 of total daily study medication dose. During the Double-blind Phase the dose range based on OxyPR was 20 – 80 mg/day, which refers to the effective, stable analgesic dose established in the Run-In period. If a dose above 80 mg oxycodone/day was needed, an uptitration to 120 mg/day oxycodone during the Double-blind Phase was permitted (100 and 120 mg/d).

Number of Subjects: It was planned that 335 subjects would be entered and approximately 200 subjects would be randomised. Actually entered: 294 subjects; randomised: 209 subjects; completed: 175 subjects.

Indication and Criteria for Inclusion: Screening Inclusion criteria included, male or female subjects of at least 18 years of age with moderate to severe chronic non-malignant osteoarthritis OA, whose primary pain site was the hip(s) and/or knee(s) and that required around-the-clock opioid therapy (oxycodone equivalent of 20-80 mg/day; who required continuation of daily opioid treatment and who were likely to benefit from WHO step III opioid therapy for the duration of the study.

Exclusion criteria included, subjects with secondary OA (e.g. fracture, septic, agromegaly), subjects with a replacement of the most painful joint, subjects with evidence of significant structural abnormalities of the gastrointestinal tract (e.g., bowel obstruction, strictures) or any diseases/conditions that affect bowel transit (e.g. ileus, hypothyroidism); Subjects with chronic disease of the joints of a relapsing/remitting nature or any other chronic condition causing pain likely to warrant the persistent use of escape analgesic (e.g. gout, Rheumatoid Arthritis (RA)).

Criteria for inclusion into the Double-blind Phase included, subjects who continued to satisfy screening inclusion/exclusion criteria, were taking OxyPR 20-80 mg/day, rated their pain (“average pain” over the last 24 hours) as ≤4 on 0-10 scale with less than or equal to two doses of oxycodone immediate release (OxyIR) rescue medication per day for either the last three consecutive days or four of the last seven days before randomisation. Subjects must also have had confirmed opioid related constipation, which was defined as having less than 3 CSBM-NS (CSBM-Non Straining) during the last 7 days before randomisation.

Test Treatment, Dose, and Mode of Administration:

Double-blind Phase

Study Medication	Dosage Form	Unit Strength	Dosing Freq.	Mode of Admin.	Batch No.
Prolonged-release oxycodone/naloxone (OXN PR)	Tablets	5/2.5, 10/5, 20/10, and 40/20 mg oxycodone/naloxone combination	q12h	Oral	5/2.5: PN3331 & PN3388 10/5: PN3351 20/10: PN3343 & PN3391 40/20: PN3282
Matched placebo for OxyPR	Tablets	Matching placebos for 5, 10, 20, and 40 mg OxyPR tablets	q12h	Oral	5: PN3423 & PN3221 10: PN3217 20: PN3218 & PN3381 40: PN3219

Reference Treatment, Dose, and Mode of Administration:

Pre-Randomisation Run-in Phase (open-label)

Study Medication	Dosage Form	Unit Strength	Dosing Freq.	Mode of Admin	Batch No.
Prolonged-release oxycodone (OxyPR)	Tablets	5, 10, 20 and 40 mg oxycodone	q12h	Oral	5: PN3352 10: PN3355 20: PN3216 & PN3354 40: PN3367

During The Run-in Period dosing was fixed and symmetrical (20, 30, 40, 50, 60, 70, 80 mg/day OxyPR).

Double-Blind Phase

Study Medication	Dosage Form	Unit Strength	Dosing Freq.	Mode of Admin.	Batch No.
Prolonged-release oxycodone (OxyPR)	Tablets	5, 10, 20 and 40 mg oxycodone	q12h	Oral	5: PN3352 10: PN3355 20: PN3216 & PN3354 40: PN3367
Matched placebo for OXN PR	Tablets	Matching placebos for 5/2.5, 10/5, 20/10, and 40/20 mg OXN PR tablets	q12h	Oral	5/2.5: PN3226 10/5: PN3228 & PN3392 20/10: PN3358 & PN3229 40/20: PN3230

During the Double-blind Phase dosing was fixed and symmetrical (20, 30, 40, 50, 60, 70, 80, 100 and 120 mg/day OxyPR for subjects receiving OxyPR and 20/10, 30/15, 40/20, 50/25, 60/30, 70/35, 80/40, 100/50 and 120/60 mg/d for subjects receiving OXN PR). However, for stepwise switch blisters for daily doses of 60/30, 70/35 and 80/40 mg/d of OXN PR, the initial naloxone dose was increased during the first days of the first week of the Double-blind Phase and could be asymmetrical.

Concomitant Medication Including Rescue:

All other medications not prohibited by the protocol and considered necessary for the subject's welfare could be administered and/or continued under the supervision of the investigator.

Rescue analgesic and laxative medication (Run-in, Double-blind)

Rescue Medication	Dosage Form	Unit Strength	Dosing Freq.	Mode of Admin.	Batch No.
Oxycodone immediate release (OxyIR; ie, OxyNorm®)	Capsules	5 mg	q4-6h PRN	Oral	PN3287
Bisacodyl	Tablets	5 mg	q3d PRN* (10mg/d)	Oral	PN3377

*OxyIR was the only allowed rescue pain medication.

Duration of Treatment:

Pre-randomisation Phase: Screening Period: up to 14 days - Run-in Period: 7 to 28 days
Double-blind Phase: Treatment with double-blind medication for 12 weeks (approximately 84 days) followed by 7 days follow-up.
Total Duration: Up to approximately 133 days

Treatment Schedule:

Pre-randomisation Phase (up to 42 days): Screening (up to 14 days): Subjects kept their pre-study medication until Visit 2.

Run-in Period (7 to 28 days): At Visit 2, subjects had their opioid therapy converted to open-label OxyPR, which was titrated to an effective analgesic dose between 20 - 80 mg/day of OxyPR. OxyIR was available as rescue medication. Subjects also had their pre-study laxative therapy converted to the study laxative (bisacodyl) to be used per the study routine for constipation during this period (no sooner than 72 hours after their most recent bowel movement (BM) as rescue medication for constipation). The 7-day baseline assessment in the Run-In Period started no sooner than the day of the initial dose conversion to OxyPR.

Double-blind Phase (12 weeks): Subjects were randomised at Visit 3 to OXN PR or OxyPR every 12 hours in a 1:1 ratio. Subjects started the Double-blind Phase at the same dose of oxycodone PR that they received at the end of the Run-in Period. The switch to double blind study medication was done over a period of 4 days within the first week of the Double-blind Phase for the 60 to 80 mg/day doses. Double-blind study medication was administered in a double-dummy manner. Subjects were permitted to take OxyIR for rescue. During the Double-blind Phase subjects were only allowed bisacodyl, as detailed previously. Other laxatives, except for fibre supplementation or bulking agents, were not permitted. If necessary, titration up to 120 mg based on oxycodone PR per day was allowed during this period, as detailed previously.

Criteria for Evaluation

Efficacy assessments included:

Primary efficacy variables:

- Patient assessment of pain and locomotor function by the Western Ontario and McMaster Universities Osteoarthritis Composite Index (WOMAC VA3.1, visual analogue scale).
- Bowel Function Index (BFI) was the mean of the following items (assessed at each visit for the last 7 days): Ease of defecation (numerical analogue scale [NAS], 0=easy/no difficulty; 100=severe difficulty), Feeling of incomplete bowel evacuation (NAS, 0=not at all, 100=very strong), Personal judgment of constipation (NAS, 0=not at all, 100=very strong).

Secondary efficacy variables:

- Pain Intensity Scale – Average Pain over the last 24 hours, as assessed at each double-blind study visit.
- PAC-SYM (Frank et al. 1999), a validated questionnaire assessing the symptoms of constipation. It is a measure of the severity of twelve symptoms of constipation over the past 7 days. Subjects completed this measure at all scheduled study visits.
- PAC-SYM(b); This is an adaptation of the PAC-SYM, which includes the first 12 questions of the validated PAC-SYM and an additional measure of bothersomeness of the symptoms of constipation.

Plus, some exploratory efficacy variables such as Complete Spontaneous Bowel Movements (CSBMs), frequency of laxative use, Modified Brief Pain Inventory Short-Form (BPI-SF), frequency of pain rescue medication use and the SF-36 v2 health survey.

Safety: Safety was assessed by documentation of adverse events, clinical laboratory results, vital signs, Subjective Opiate Withdrawal Scale (SOWS) and electrocardiograms (ECGs) and recorded on the standard CRF pages and SAE data form.

Statistical Methods:

Primary Efficacy Analyses: The primary analysis is given by an intersection-union test that combines a non-inferiority hypothesis test in the WOMAC VA3.1 visual analogue scale score (showing that the efficacy of OXN PR is at least 80% that of OxyPR) with a superiority test in the BFI (showing that OXN PR is superior to OxyPR with respect to the BFI). The combined test was carried out separately for each of the double-blind visits (4-8) as long as all subsequent or later visits also rejected the null-hypothesis. This, again, is an intersection-union test across the various visits, so that the analysis kept a multiple 5% significance level at all times.

Secondary Efficacy Analyses: PAC-SYM, PAC-SYM (b) and the average pain over the last 24 hours were analysed by means of mixed model repeated measures (MMRM) analysis of covariance with change of the visits 4 - 8 to baseline value as the repeated measures. Thereby, the baseline value is the outcome at Visit 3 of the assessed variable, respectively. For any discontinuation after Visit 4 the value from the discontinuation visit is used as a substitute for the value at the next scheduled visit. Apart from these imputations, other values could remain missing for the MMRM analysis. The repeated measures analysis included terms for treatment, country, and time as categorical variables, and the baseline value as a continuous covariate. Because the number of subjects within each centre was expected to be small, the effect of centre was not included in any of the analyses below, however country was used as a factor.

For exploratory efficacy analyses the number of CSBMs, the frequency of laxative intake, that of rescue medication intake, the modified BPI-SF subscales and the SF- 36 v2 quality of life assessment were carried out by means of descriptive sample statistics. In case of any interesting findings, model-based analyses could be added but were recognized in a purely exploratory manner only.

Results: The study population comprised 59 male and 150 female subjects with a mean age of 63 years (range 29-84 years). The majority (99.5%) were Caucasian. Based on medical history data in the double-blind safety population, 67.9% of subjects had hypertension and 22.5% of subjects had spinal OA. All subjects had constipation and OA as these were inclusion criteria. There were no notable differences between the treatment groups in subject demographics or baseline characteristics. 175 (83.7%) of subjects completed the study; 88 (87.1%) in the OXN PR group and 87 (80.6%) in the OxyPR group. The main reason for discontinuation was AEs (23 (11.0%) in total, 9 (8.9%) in the OXN PR group and 14 (13.0%) in the OxyPR group.

Efficacy: Note that Visit 3 occurred at baseline (end of run-in) and Visit 8 was the end of double-blind phase.

Primary endpoints

The summary WOMAC scores for pain, stiffness and difficulty performing daily activities decreased in both groups by the end of the study in both the FA and the PP population, indicating an improvement in these symptoms and activities. The scores for each section score (pain, stiffness, difficulty performing daily activities) decreased by similar amounts in both groups (Pain: Visit 3, Mean (SD) 207.5 (90.28) for OXN PR, 214.4 (80.75) for OxyPR & Visit 8, Mean (SD) 181.0 (97.22) for OXN PR, 198.3 (98.75) for OxyPR; Stiffness: Visit 3, Mean (SD) 90.1 (40.17) for OXN PR, 97.6 (39.13) for OxyPR & Visit 8, Mean (SD) 79.2 (41.93) for OXN PR, 86.2 (40.07) for OxyPR; Daily Activities: Visit 3, Mean (SD) 806.5 (312.67) for OXN PR, 871.9 (311.74) for OxyPR & Visit 8, Mean (SD) 700.8 (356.73) for OXN PR, 772.8 (352.81) for OxyPR; (FA population)). Although there was a difference in the 'difficulty performing daily activities' score between the groups at Visit 3, where the score was lower in the OXN PR group, this difference was maintained at Visit 8, showing that the size of the reduction was similar between groups. The statistical analysis of the WOMAC OA index showed that OXN PR was non-inferior to OxyPR

Mean BFI scores for Visit 3 to Visit 8 were as follows: (BFI by Visit with LOCF) Visit 3, Mean (SD) 55.8 (21.34) for OXN PR and 57.9 (18.66) for OxyPR & Visit 8 Mean (SD) 30.1 (25.14) for OXN PR and 38.0 (25.61) for OxyPR. At Visit 8 OXN PR was statistically significantly superior to OxyPR (95% CI: -13.8, -0.52). Similar results were seen for the BFI by Visit, Observed Values. These results show that the primary objectives of this study were met.

Secondary endpoints

The scores for average pain over the last 24 hours were similar between groups at Visit 3 (mean (SD) 3.6 (1.21) for OXN PR; 3.6 (1.08) for OxyPR) and remained constant by Visit 8 (mean (SD) 3.7 (1.67) for OXN PR; 3.8 (1.75) for OxyPR) indicating that both treatments were effective in the management of pain (estimate for treatment difference at Visit 8 was -0.11 (95% CI -0.42, 0.21).

The sum of scores for the PAC-SYM(b) questionnaire with regards symptoms, degree of bothersomeness and frequency, all decreased from Visit 3 to Visit 8 for both of the groups (Symptoms: Visit 3, Mean (SD) 16.1 (8.36) for OXN PR and 16.1 (7.89) for OxyPR & Visit 8, Mean (SD) 8.8 (8.32) for OXN PR and 10.0 (8.33) for OxyPR; Degree of Bother: Visit 3, Mean (SD) 15.8 (9.41) for OXN PR and 15.8 (8.45) for Oxy PR & Visit 8, Mean (SD) 8.9 (8.70) for OXN PR and 9.7 (8.82) for OxyPR; Frequency: Visit 3, Mean (SD) 4.4 (1.82) for OXN PR and 4.4 (1.66) for OxyPR & Visit 8, Mean (SD) 2.3 (2.10) for OXN PR and 2.9 (2.08) for OxyPR). The difference between the two groups was as follows, for Symptoms: estimate for treatment difference at Visit 8 was -1.48 (95% CI -3.01, 0.04); for Degree of Bother: estimate for treatment difference at Visit 8 was -1.42 (95% CI -3.09, 0.25); for Frequency: estimate for treatment difference at Visit 8 was -0.44 (95% CI -0.88, 0.00).

Exploratory endpoints

By the end of the study there was no real difference in BPI-SF score between the OXN PR and the OxyPR group. Rescue medication use was very low overall and there was no difference between groups in the mean daily dose, frequency, or number of days on which rescue was taken. The SF-36 health survey showed that scores tended to improve with treatment but there was no obvious difference between the groups for any particular aspect of the survey. Laxative intake was slightly lower from Visit 3 to Visit 8 in the OXN PR group compared to the OxyPR group and this difference was greatest by Visit 8, where the number of subjects who had laxative intake was 39 (38.6%) in the OXN PR group and 56 (51.9%) in the OxyPR group, compared to 56 (55.4%) in the OXN PR group and 69 (63.9%) in the OxyPR group respectively at Visit 3. Finally, no difference was seen in the number of CSBMs between the groups.

Safety: The number of subjects completing ≥ 84 days of treatment in the Double-blind Phase was 80 (79.2%) in the OXN PR group and 76 (70.4%) in the OxyPR group and the median extent of exposure for the total safety population was 85 days.

Adverse events were reported by a similar number of subjects in the OXN PR group (67 (66.3%)) and the OxyPR group (70 (64.8%)). The most common AEs (reported by more than 10% of subjects) were gastrointestinal (GI) disorders (21 subjects (20.8%) in the OXN PR group and 17 subjects (15.7%) in the OxyPR group)), investigations (35 subjects (34.7%) in the OXN PR group, (including 8 subjects with increased blood glucose and 12 with decreased lymphocyte count) and 30 subjects (27.8%) in the OxyPR group (including 7 subjects with increased blood glucose and 2 with decreased lymphocyte count)), metabolism and nutrition disorders (19 subjects (18.8%) in the OXN PR group and 18 subjects (16.7%) in the OxyPR group) and nervous system disorders (10 subjects (9.9%) in the OXN PR group and 12 subjects (11.1%) in the OxyPR group). The number of subjects reporting gastrointestinal (GI) AEs was similar for both treatment groups (21 subjects (20.8%) in the OXN PR group and 17 (15.7%) subjects in the OxyPR group).

The number of subjects with treatment-related AEs (i.e. AEs considered unlikely, possibly, probably and definitely related to study medication by the Investigator) was slightly higher in the OxyPR group (29 subjects (28.7%) in the OXN PR group and 40 (37.0%) in the OxyPR group). Treatment-related AEs reported for ≥2% of subjects were diarrhoea (3 (3.0%) with OXN PR and 2 (1.9%) with OxyPR), nausea (6 (5.9%) with OXN PR and 1 (0.9%) with OxyPR) vomiting (4 (4.0%) with OXN PR and 1 (0.9%) with OxyPR), dizziness (0 with OXN PR and 5(4.6% with OxyPR) and hyperhidrosis (4 (4.0%) with OXN PR and 4 (3.7%) with OxyPR).

The majority of AEs were mild or moderate in nature. Severe AEs were reported by only 15 subjects (7.2%). Of these, 4 (4%) subjects were in the OXN PR group (including abdominal pain (2), drug withdrawal syndrome (1) colon cancer (1) and hot flush (1)) and 11 (10.2%) subjects were in the OxyPR group (constipation (1), bile duct stone (1), alanine aminotransferase increased (1), aspartate aminotransferase increased (1), gamma-glutamyltransferase (GGT) increased (2), back pain (1), intervertebral disc protrusion (1), neck pain (1), restlessness (1) and hypertension (1)). Note, a subject could be counted more than once if they had more than one AE.

There were no deaths during the double-blind phase of the study, however one subject died from urinary tract infection leading to urosepsis, septic shock and multi-organ failure while they were in the pre-randomisation phase and receiving OxyPR. This fatal AE was not suspected to be related to study medication. Eight (3.8%) randomised subjects experienced SAEs (3 (3.0%) in the OXN PR group and 5 (4.6%) in the OxyPR group) and 11 subjects who were not randomised experienced SAEs. In the OXN PR group only one of these subjects had SAEs considered as related to study medication (hypertension crisis and drug withdrawal syndrome, both probably related to study medication as assessed by the investigator, the Sponsor considered the hypertension crisis to be possibly related). In the OxyPR group three subjects had SAEs that were considered as related to study medication (jaundice cholestatic - possibly related (one subject); vertigo - probably related, hyperhydrosis, palpitations and tremor – all definitely related as assessed by the Investigator and probably related as assessed by the Sponsor (one subject); hypertension – unlikely to be related (one subject)). In addition, one SAE was considered to be related to pre-randomisation study medication (OxyPR) in a subject who was not randomised (nausea – definitely related as assessed by the Investigator and probably related as assessed by the Sponsor). The Sponsor considered a further SAE in the pre-randomisation phase to be possibly related to OxyPR, which the Investigator had assessed as not related (epileptic seizure).

The most common reason for discontinuation was AEs (23 (11.0%) in total, 9 (8.9%) in the OXN PR group and 14 (13.0%) in the OxyPR group. AEs were reported during the double blind phase by a similar number of subjects in the OXN PR group (67 (66.3%)) and the OxyPR group (70 (64.8%)). AEs leading to discontinuation for more than one subject in the OXN PR group were abdominal pain (3 subjects) diarrhoea (2 subjects) and nausea (2 subjects); AEs leading to discontinuation for more than one subject in the OxyPR group were constipation (2 subjects) and GGT increased (2 subjects). The majority were considered as treatment-related (definitely, probably, possibly or unlikely to be related to study medication).

There were no clinically notable changes in mean vital signs values over the course of the study in either treatment group. Analyses of haematology and biochemistry parameters did not reveal any clinically notable changes in the mean values over the course of the study in either treatment group. Out of range values were observed for some laboratory parameters, but no trend of shifts in one particular direction was identified for any parameter in either treatment group. ECG changes were infrequent and isolated, and no ECG abnormality was directly attributable to study medication.

Conclusions:

This study shows that OXN PR is non-inferior to OxyPR in the management of pain and locomotor function in subjects with moderate to severe pain. This finding is supported by WOMAC scores for pain, stiffness and difficulty performing daily tasks, and by the similar BPI scores between groups and the low use of rescue medication overall.

OXN PR was also shown to be statistically significantly superior to OxyPR at Visit 8 with regards to improvements in symptoms of constipation. In addition, OXN PR was associated with a lower laxative intake. The quantitative assessment provided inconclusive results, with a confidence interval ranging from minor to major treatment effects (95% CI: - 13.8, -0.52), but a more informative assessment than this was beyond the scope of this particular study. Such an assessment would require a much bigger sample size and greater control of the placebo effect, which is still suspected to obscure treatment effects at Visit 8 in this study and should be investigated more thoroughly in future studies. Now that OXN PR has been proven to demonstrate a valid effect against OA pain, it can be assumed that the relevant effects seen in other OXN PR studies in different types of pain, can also be assumed here.

The most frequent treatment-related AEs were consistent with the known safety profile of the opioid analgesic class of drugs.The incidence of AEs was in general similar between groups however there were slightly higher numbers in the OxyPR group with regards severe AEs, SAEs and withdrawals from the study.

The primary objectives of this study were met and were supported by further pain score assessments and a lower use of rescue medication in the OXN PR group.

Date of the Report: 29 February 2012