## 2. SYNOPSIS

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| **Name of Company:** Mundipharma Research GmbH & Co. KG | INDIVIDUAL STUDY TABLE | (For National Authority Use Only) |
| **Name of Finished Product:** Oxycodone/naloxone prolonged release tablets (OXN PR) | Referring to Part IV of the Dossier | |
| **Name of Active Ingredient:** Oxycodone/naloxone combination | Volume: Page: | |

**Title of the Study:** A randomised, double-blind, double-dummy, parallel-group multicentre study to demonstrate improvement in symptoms of constipation in subjects with non-malignant pain taking oxycodone equivalent of 60 - 80 mg/day as oxycodone / naloxone prolonged release (OXN PR) compared to subjects taking oxycodone prolonged release tablets (OxyPR) alone.

**Investigator(s)/Centre(s):** Principal Co-ordinating Investigator (German LKP): Oliver Loewenstein MD, Germany: 86 sites;, Czech Republic: 13, Finland: 3, Hungary: 2; Germany: 47, Netherlands: 4; UK: 11, Spain: 6

**Publication (Reference):** None

| **Study Dates:** | **Study Status:** | **Phase of Development:** |
|---|---|---|
| 26-May-2006 to 12-Jul-2007 | Completed | Phase 3 |

**Objectives:** The primary objective of this study was to demonstrate that subjects with moderate to severe non-malignant pain taking oxycodone/naloxone prolonged release tablets (OXN PR) had improvement in symptoms of constipation as measured by the bowel function index (BFI) compared to subjects taking oxycodone prolonged release tablets (OxyPR) 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 as measured by the Pain Intensity Scale; to demonstrate that subjects receiving OXN PR have improvements in symptoms of constipation as measured by the Patient's Assessment of Opioid induced Constipation (PACOI) compared to subjects taking OxyPR; to compare the subject's overall opinion of their improvement with treatment over the course of the Double-blind Phase following treatment with OXN PR compared with OxyPR as measured by the Patient Global Impression of Change; to assess subject's assessment of opioid-induced constipation, constipation symptom severity, impact and bothersomeness based on the PAC SYM(b).

**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 who met 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 OxyPR, which was titrated to an effective analgesic dose between 60 - 80 mg/day of OxyPR. Oxycodone immediate release (OxyIR) was available as rescue medication. Subjects also had their pre-study laxative therapy converted to the study laxative that was used as 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). [*Added by Amendment 3 (dated 07-Dec-2006): However, investigators were to instruct their subjects that if they exhibit discomfort during the 72 hours period they could take oral bisacodyl as a laxative earlier than 72 hours after their most recent BM as required to treat constipation. The maximum allowed number of bisacodyl intakes was 5 dosages bisacodyl 10 mg/day (see Section 9.5.1.4.) 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 within the first week of the double-blind phase. During the double-blind phase the subjects continued to use study laxatives as per the study design described above. 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.

At the randomisation to the Double-blind phase the dose range based on oxycodone PR was 60 – 80 mg/day, which refers to the effective, stable analgesic dose established in the Run-In period. If a dose above 80 mg oxycodone PR/day was needed, an uptitration to 120 mg/day oxycodone PR during the Double-blind Phase was permitted.

Extension Phase (up to 52 additional weeks):

At Visit 9, subjects meeting the Extension Phase Entrance Criteria (i.e., complete the Double-blind Phase) had the option to receive open-label OXN PR for up to 52 additional weeks during the Extension Phase. Dose titration was permitted at the discretion of the Investigator. OxyIR was prescribed as rescue medication only for the first week of the Extension Phase up to 6 times a day at a dose of approximately 1/6 of total daily study medication dose. Subjects entering the Extension Phase were treated with the oxycodone PR dose, which was necessary for adequate analgesia at the end of the double-blind phase. Subjects were switched in an open-label stepwise manner over the period of 4 days within the first week of the extension phase to the corresponding OXN PR dose. An uptitration to 120/60 mg/day OXN PR was allowed.

**Number of Subjects:** Planned: 266 randomised subjects. Screened: 379, Enrolled: 347 subjects. Run-in safety: 331 subjects; Randomised: 278 subjects. Full analysis: 265 subjects. Double-blind Safety: 265. Per Protocol: 193. Completed 222 subjects.

**Indication and Criteria for Inclusion:**

**Screening Inclusion criteria**:

1. Males and females, 18 years of age or older.
2. Documented history of moderate to severe nonmalignant pain that require around-the-clock opioid therapy (oxycodone equivalent of 60 – 80 mg/day).
3. Subjects with constipation caused or aggravated by an opioid.
4. Subjects willing and able to participate in all aspects of the study and willing to discontinue their current opioid analgesic routine, laxative regimen, and comply with the use of oral bisacodyl as laxative rescue medication.
5. Subjects taking pre-study, non-opioid analgesics, and all other concomitant medications, including those medications for the treatment of depression, that are thought to be stable, and are considered necessary for the subject's welfare, and are anticipated to remain stable throughout the Double-blind Period of the study, and are to be continued under the supervision of the investigator, are eligible.

**Screening Exclusion criteria:**

1. Females who are pregnant (positive β-hCG test) or lactating.
2. Subjects with any contraindication to bisacodyl or any history of hypersensitivity to oxycodone, naloxone, or related products. [Changed according to Amendment 2 (dated 27-Mar-2006) in subjects with any contraindication to bisacodyl or any history of hypersensitivity to oxycodone, naloxone, related products, and other ingredients.]
3. Subjects with evidence of any clinically unstable disease or subjects with evidence of impaired liver/kidney function upon entry into the study.
4. Subjects with evidence of significant structural abnormalities of the gastrointestinal tract or any diseases/conditions that affect bowel transit.
5. Subjects who have required treatment for the diagnosis of irritable bowel syndrome (IBS); Surgery within 2 months prior to the start of the Screening Period, or planned surgery during the12-week Double-blind Phase that may affect GI motility or pain.
6. Subjects with cancer associated pain.
7. Subjects with Rheumatoid Arthritis (RA)
8. Subjects receiving opioid substitution therapy for opioid addiction (e.g., methadone or buprenorphine)
9. Subjects with active alcohol or drug abuse and/or history of drug (opioid)/alcohol abuse. [*Adapted <u>only</u> for Germany according to Local Amendment 1 (dated 27-Mar-06): Subjects with a positive urine drug test at screening visit 1, which indicates unreported illicit drug use or unreported use of a concomitant medication not required to treat the subjects medical condition(s).]*

*[Added according to Amendment 2 (dated 27-Mar-2006)*

10. *Subjects with any situation in which opioids are contraindicated, severe respiratory depression with hypoxia and/or hypercapnia, severe chronic obstructive lung disease, cor pulmonale, severe bronchial asthma, paralytic ileus*
11. *Subjects with myxoedema, hypothyroidism, Addison`s disease, increase of intracranial pressure and/or epilepsy]*

**Additional Criteria for entry to the Double Blind phase:**

1. Subjects continue to satisfy Screening Inclusion/Exclusion criteria.
2. Subject's OxyPR dose must be between 60- 80-mg/day.
3. Subjects must rate their pain ("average pain" over the last 24 hours) as ≤4 on 0-10 Numeric rating scale scale with less than or equal to two doses of oxycodone immediate release (OxyIR) rescue medication per day (Appendix, Section 12.6 of Protocol for doses of OxyIR) for <u>either</u> the last three consecutive days <u>or</u> four of the last seven days.
4. Subjects must have confirmed opioid related constipation, which is defined as having less than 3 CSBM-NS during the last 7 days.
5. Subjects demonstrate compliance with laxative use, taking open-label OXY, and completing daily diaries.

**Test Treatment, Dose, and Mode of Administration:** Double-blind Phase: Oxycodone/naloxone prolonged release tablets (OXN PR) 10/5, 20/10 and 40/20 mg taken orally.

**Reference Treatment, Dose, and Mode of Administration:** Double-blind Phase: Oxycodone prolonged release tablets (OxyPR) 10, 20 and 40 mg taken orally.

**Duration of Treatment:** Pre-randomisation Phase: Screening may last up to 14 days, and Run-in Period may last 7 to 28 days. Double blind Phase: 12 weeks.

Treatment Schedule:

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 Period (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 60 - 80 mg/day of OxyPR. 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). 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 in a 1:1 ratio to OXN PR or OxyPR at visit 3. Subjects started the Double-blind Phase at the same dose of OxyPR 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. The first dose of Double-blind medication was taken by subjects on the evening of Visit 3. Double-blind study medication was administered in a double-dummy manner. Subjects were permitted to take OxyIR for rescue; it could be dosed every 4 hours as needed at doses detailed in Section 12.6 of the Protocol. During the Double-blind Phase subjects followed the laxative regimen as detailed for the run-in period. Other laxatives, except for fiber supplementation or bulking agents, were not permitted.

If necessary, titration up to 120 mg based on oxycodone prolonged-release per day was allowed during this period (see also section: Study Design Methodology of the Protocol).

**Criteria for Evaluation:**

Efficacy Assessment(s):

Efficacy assessments were collected in daily diaries and during periodic visits.

Primary efficacy variable:

- Bowel Function Index (BFI) was the mean of the following items (assessed at each visit): 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:

- Patient assessment of opioid-induced constipation (PACOI, the mean of the summary scores from the rectal and stool subscales of the PAC-SYM)
- Patient Global Impression of Change (PGIC); Subjects rated their overall opinion of their improvement with treatment over the course of the Double-blind Phase on a scale of 1 – 7 (1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, 7 = very much worse).
- Pain Intensity Scale – Average Pain over the last 24 hours, as assessed at each double-blind study visit.
- PAC-SYM(b); This is an adaptation of the PAC-SYM (Frank et al. 1999[5]), which includes the first 12 questions of the validated PAC-SYM and an additional measure of bothersomeness of the symptoms of constipation. For each symptom, the subject was asked to grade both the severity of the symptom and the degree of bothersomeness of the symptom. Severity was rated on a 5-point scale, where 0 = absent and 4 = very severe. Bothersomeness was rated on a 5-point scale, where 0 = not at all and 4 = extremely. There was one additional question at the end, assessing the frequency of bowel movements in the past 7 days. Each subject was asked if he/she had fewer bowel movements than they would have liked over the past 7 days, where 0= none of the time and 4 = all of the time. They were then be asked how bothered they were about the frequency, where 0 = not at all and 4 = extremely.

Exploratory efficacy variables:

Subject Bowel Function Measures (number, consistency, completeness of bowel movements, and laxative intake before bowel movement), Complete spontaneous bowel movements (CSBMs), Complete Spontaneous Bowel Movements – No straining, no diarrhoeal (CSBM-NS, ND), Spontaneous Bowel Movement (SBM), Treatment satisfaction questionnaire for Medication (TSQM), SF-36 v2, Pain Intensity Scale – Average Pain over the last 24 Hours (assessed at each diary day), rescue medication intake (mean across the double-blind phase).

Drug Concentration Measurements:

Blood samples for PK analysis were obtained during Visits 4, 6, and 8/early discontinuation.

Bioanalytical Methods:
Plasma samples were analysed for plasma concentrations of oxycodone, naloxone and metabolites using a previously validated analytical method.

Safety:
Safety was assessed by analysing spontaneously reported adverse events, clinical laboratory results, vital signs, physical examinations, and electrocardiograms (ECGs) and the Modified Subjective Opioid Withdrawal Scale (SOWS).

**Statistical Methods:**

Efficacy Analyses:

For the primary efficacy endpoint, a mixed-model repeated measures (MMRM) analysis of covariance of the BFI was carried out for Days 8, 15, and 29 as the repeated measures. If the subject discontinued prior to Day 8 then the value from the discontinuation visit was employed as a substitute for the value from Day 8. For any discontinuation after Day 8, the value from the discontinuation visit was used as a substitute for the value at the next scheduled visit. Apart from these imputations, other values may have remained missing for the MMRM analysis. The repeated measures analysis included terms for treatment, country, and time as a categorical variable, and pre-randomisation value at the end of the Baseline Period. 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 the PACOI, PAC-SYM, Pain Intensity Scale – Average Pain over the last 24 hours (for the diary pain intensity scale the average of the last seven day before each visit was taken) the same methodology as for the BFI was applied.

The analysis of the PGIC, TSQM, and rescue medication intake followed an ANOVA methodology with terms for treatment and country. For CSBM analysis two responder variables were defined. A CSBM1 responder was a subject who had an improvement of at least one CSBM at the end of the double-blind phase compared to pre-randomisation. A CSBM3 responder was defined as a subject who had at least 3 CSBM at the end of the double-blind phase. Both CSBM responder variables were analysed by comparing their relative risks and calculating the odds ratio using negative binomial regression.

Both treatments were compared by statistical hypothesis tests which were conducted at the two-sided 0.05 level of significance. Confidence intervals (95%) for the difference between treatment means were displayed wherever possible.

All efficacy analyses were performed using the Full Analysis population. The primary analysis on bowel function and the analysis of the pain intensity scale were also performed on the Per-Protocol population

**Results:**

**Efficacy:**

The comparison of mean BFI scores after 4 weeks of the double-blind phase was the primary analysis for the primary objective of this study. At Visit 3 bowel function was comparable between both groups (mean (SD) of 64.04 (19.84) in the OxyPR group and 67.4 (19.51) in the OXN PR group) but after four weeks (by Visit 6) mean BFI had improved considerably in the OXN PR group (40.94 (27.38)) and this reduction of 26.46 points in the BFI score was clinically relevant. In the OxyPR group there was a reduction in mean BFI score between Visit 3 (64.04 (19.84)) and Visit 6 (53.27 (23.86)) but this reduction of 10.77 points was not clinically relevant (change in the BFI score > 12).

This improvement in mean observed BFI score was seen early on in the double-blind phase. By Visit 4, just 1 week after randomisation, the mean BFI score in the OXN PR group had already reduced by 23.24 points to 44.16 (26.53), while at the same time point, the mean BFI score in the OxyPR group had only reduced by 6.13 points to 57.96 (21.49). The reduction in mean BFI score continued past the 4 week stage to the end of the study (Visit 8) at which time there was still a clinically relevant difference in BFI score between the groups in favour of the OXN PR group. Mean observed values at Visit 8 were 48.63 (28.8) in the OxyPR group vs 34.01 (29.31) in the OXN PR group. Also, the improvement in mean observed BFI scores within the OXN PR group, from a baseline of 67.4 (19.51), to the end of double-blind period value of 34.01 (29.31), is clinically relevant (a mean reduction of 33.39 points on the BFI score).

These results confirm the superiority of OXN PR over OxyPR based on primary analysis of the BFI.

The decrease of the mean (SD) PACOI values from baseline (V3) to V6 was more pronounced in the OXN PR group compared to the OxyPR treatment group. At V6 the mean (SD) PACOI describing bothersomeness was 1.07 (0.78) in the OxyPR group, whereas the value in the OXN PR treatment group was 0.75 (0.70). The corresponding PACOI – symptom value was 1.12 (0.75) in the OxyPR group and 0.79 (0.65) in the OXN PR group. The difference between the two groups was statistically significant in favour of the OXN PR group for both PACOI subscores (bothersomeness and Symptoms) (PACOI-Bothersomeness: OXN PR vs OxyPR: -1.93; $p<0.0001$; CI, -2.34, -1.52; PACOI-Symptoms: OXN PR vs OxyPR: -1.89; $p<0.0001$; CI, -2.27, -1.51).

As before, this reduction in score was already visible in the OXN PR group by Visit 4. The difference between the groups was still present by Visit 8.

Subjects in the OXN PR group had a statistically significantly increased number of complete spontaneous bowel movements (CSBMs) after 4 weeks in the double-blind phase (Visit 6) compared to subjects in the OxyPR group (OXN PR vs. OxyPR: 0.46; $p<0.0001$; CI, 0.37, 0.58). The difference was approx. 1.27 CSBM per week in the Oxycodone/Naloxone PR group and is particularly relevant for a chronic treatment.

The PAC-SYM and PAC-SYM(b) scores mirrored each other and correlated with the results of the primary efficacy analysis (BFI scores) in showing that constipation symptoms and bothersomeness were statistically significantly reduced by Visit 6 in the OXN PR group compared to the OxyPR group (for PAC-SYM, $p<0.0001$ by Visit 6). An improvement was noted in the OXN PR group as early as Visit 4, 1 week after the start of the double-blind phase and the reduction in scores continued through to the end of the double-blind phase.

Pain Intensity Scale scores (and daily scores) were comparable between groups and remained constant throughout the double-blind phase. These results, combined with the TSQM and SF36 overall health scores, and the PGIC scores, which were also comparable between groups throughout the study, as well as the low level of supplemental analgesic use in both groups, further support the finding of analgesic equivalence between OxyPR and OXN PR.

The results of the extension phase of this study will be presented in a separate report (OXN3006S).

**Pharmacokinetic:** The Pharmacokinetic results of this study are presented in a separate report.

**Safety:** There were no deaths reported in this clinical trial. 16 subjects experienced 21 serious adverse events. One SAE was rated as probably being related to OXN PR therapy /bile duct obstruction), 3 SAEs (grand mal convulsion with consecutive skin laceration, pneumonia) were considered to be possibly related by the investigator. One additional SAE (cholecystitis acute) was assessed as possibly related by the Sponsor. All of these occurred in the OXN PR group. Convulsions and biliary colic have been added as potential ADRs to the OXN product information, for oxycodone these are already known potential ADRs. All other SAEs were assessed as being unrelated or unlikely related to the study medication.

71 subjects (52.6%) in the OxyPR group and 82 (63.1%) in the OXN PR group experienced adverse events. The most frequently reported AEs were abdominal pain, nausea, pain and headache in the OXN PR group and nausea, pain, back pain and headache in the Oxy PR group.

On the first day after randomisation the mean SOWS values were comparable in both treatment groups. The mean SOWS values remained stable during the first 7 days of the double-blind phase, indicating that drug withdrawal was not a problem after the switch to study medication in the double-blind phase.

Some subjects had abnormal laboratory values, but no trends in the overall patient population with respect to lab value changes were observed. Changes in lab values were not attributed to the study drug.

Vital sign changes were isolated and not considered clinically important by the Investigator. Based on the vital sign data available in this study, no vital sign abnormality was directly attributable to study drug.

ECG abnormalities observed during the study were either observed at baseline, or were observed in subjects with known ECG abnormalities.

Despite the acknowledgement of a formally higher number of AEs in the OXN PR treatment group, upon deeper analysis of the respective events or suspected adverse drug reaction there are no safety concerns arising from the use of higher doses of OXN PR tablets. Either the observed AEs were more likely caused by the individual patients' medical history or the underlying disease or with respect to the gastrointestinal ADRs could be attributed to the onset of naloxone effect in severely constipated patients and were reported to be of short duration.
Importantly, there were no new or unexpected adverse reactions observed which were attributable to the administration of OXN PR in higher doses. Therefore, the safety profile of OXN PR in the investigated doses is consistent with those of other strong opioids.

It is also important to mention that "constipation" as a typical opioid induced ADR was not documented as AE in this study as it was an inclusion criterion. In so far a potentially beneficial safety profile of OXN PR with respect to the number of reported AEs could not be evaluated as in other clinical trials with OXN PR. In this study the beneficial effect of OXN PR on the gut was evaluated with BFI and CSBM as efficacy parameter and clearly provides evidence of the benefit of OXN PR to the investigated subjects. This beneficial effect outweighs the initial increase in abdominal symptoms in constipated patients who are switched from a strong opioid to OXN PR tablets.

**Conclusions:**

This study provides evidence that OXN PR is superior to OxyPR with regards to bowel function, and particularly with regards to reducing constipation. The difference is statistically and clinically significant. This improvement in bowel function is achieved without sacrificing any of the analgesic efficacy of the oxycodone component.

The incidence of adverse events was higher in the OXN PR group compared to the OxyPR group. The most frequently reported adverse events are consistent with the expected adverse event profile of the opioid analgesic class of drugs.

Importantly, the incidence of diarrhoea was generally low, and incidences were transient in duration and comparable between groups. SOWS sumscores were not exacerbated in the OXN PR group. After the administration of OXN PR there were no additional or unexpected risks observed when compared to OxyPR treatment. In consequence, a favourable benefit to risk ratio could be demonstrated for OXN PR in this clinical study for the investigated indication.

**Date of the Report:** 22-Feb-2008