2. SYNOPSIS

Name of Company: Mundipharma Research GmbH & Co. KG	INDIVIDUAL STUDY TABLE	(For National Authority Use Only)
Name of Finished Product:	Referring to Part IV of the Dossier	
Name of Active Ingredient: Oxycodone/naloxone combination	Volume: Page:	
Title of the Study: A randomised, double-blind, parallel-group, multicentre study to demonstrate improvement in symptoms of constipation in subjects with non-malignant pain taking oxycodone equivalent of ≥20 mg/day and ≤50 mg/day as oxycodone/naloxone prolonged-release compared to subjects taking oxycodone prolonged-release tablets alone.		
Investigator/Centre: 93 sites: UK 49; Germany 28; Spain 6; Czech Republic 10.		
Publication (Reference): None		
Study Dates: 05 January 2006 to 23 April 2007 (FPFV to LPLV)	**Study Status:** Completed	**Phase of Development:** 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 (PR) tablets have improvement in symptoms of constipation as measured by the bowel function index (BFI) compared to subjects taking oxycodone prolonged-release tablets alone.		
Methodology: This was a randomised, double-blind, double-dummy, parallel group, multicentre, 12-week study to assess the safety and efficacy of Oxycodone/Naloxone PR compared to Oxycodone PR in relieving opioid-related constipation in subjects currently taking oxycodone equivalent of ≥20 mg/day and ≤50 mg/day.		
Number of Subjects: Planned: 272 randomised subjects. Screened: 597, Enrolled: 525 subjects. Run-in safety: 524 subjects; Randomised: 322 subjects. Full analysis: 316 subjects. Completed 277 subjects.		

Indication and Criteria for Inclusion: Screening Inclusion criteria:
Males and females, 18 years of age or older with documented history of moderate to severe nonmalignant pain that required around-the-clock opioid therapy (oxycodone equivalent of ≥20 mg/day and ≤50 mg/day) who had constipation caused or aggravated by an opioid and who were likely to benefit from WHO step III opioid therapy for the duration of the study; 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; Subjects taking pre-study, non-opioid analgesics, and all other concomitant medications, including those medications for the treatment of depression, that were thought to be stable, and were considered necessary for the subject's welfare, and were anticipated to remain stable throughout the Double-blind Period of the study, and were to be continued under the supervision of the investigator, were eligible.

Screening Exclusion criteria:
Females who were pregnant (positive β-hCG test) or lactating; Subjects with evidence of clinically unstable disease or subjects with evidence of impaired liver/kidney function upon entry into the study; Subjects with evidence of significant structural abnormalities of the gastrointestinal tract or any diseases/conditions that affected bowel transit, and subjects who had 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 the 12-week Double-blind Phase that may have affected GI motility or pain. Subjects with cancer associated pain; Subjects with Rheumatoid Arthritis (RA); Subjects receiving opioid substitution therapy for opioid addiction (e.g., methadone or buprenorphine); Subjects with active alcohol or drug abuse and/or history of opioid abuse.

Criteria for entry to the Double-Blind phase:
Subjects continued to satisfy screening criteria outlined in the protocol; Subject's OXY dose was between 20-50-mg/day; Subjects 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 (Appendix, Section 12.6 for doses of OxyIR) for either the last three consecutive days or four of the last seven days; Subjects must have had confirmed opioid-related constipation, which was defined as having less than 3 CSBM-NS during the last 7 days of the Run-in Period; Subjects demonstrated compliance with laxative use, taking open-label Oxycodone PR, and completing daily diaries.

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

Extension Phase: Oxycodone/naloxone prolonged-release tablets (OXN) 10/5, 20/10, and 40/20 mg taken orally

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

Extension Phase: None

Duration of Treatment: Pre-randomisation Phase: Screening could last up to 14 days, and Run-in could last 7 to 28 days. Double-Blind Phase: 12 weeks. Extension Phase: Up to 52 weeks

Treatment Schedule: Pre-randomisation Phase (up to 42 days):

Screening (up to 14 days): At Visit 1, after written informed consent is obtained, subjects underwent complete evaluation for study eligibility (i.e., all inclusion/exclusion criteria). Subjects who met the Prospective Assessment Criteria could continue in the study.

Run-in (7 to 28 days): At Visit 2, subjects had their opioid therapy converted to open-label oxycodone prolonged-release (OXY), which was titrated to an effective analgesic dose between 20- and 50-mg/day of OXY. 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). *Added by Amendment 3 (dated 7 December 2006): However, investigators instructed their subjects that if they exhibited 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 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 OXY.

Double-blind Phase (12 weeks):

At Visit 3, subjects who qualified for entry into the Double-blind Phase of the study were randomised to Oxycodone/Naloxone PR or Oxycodone PR. Dose adjustments, if needed, were allowed during this period. Subjects received double-blind study medication for up to 12 weeks.

Extension Phase (up to 52 additional weeks):

At Visit 9, subjects who met the Extension Phase Entrance Criteria (i.e., complete the Double-blind Phase) had the option to receive open-label Oxycodone/Naloxone PR for up to 52 additional weeks during the Extension Phase. Dose titration was permitted at the discretion of the Investigator.

Criteria for Evaluation:

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

Primary efficacy variable:

- Bowel Function Index (BFI)

Secondary efficacy variables:

- Subject assessment of opioid-induced constipation (PACOI)
- Subject Global Impression of Change (PGIC)
- Pain Intensity Scale – Average Pain over the last 24 Hours, as assessed at each double-blind study visit.

Pharmacokinetic: Blood samples for pharmacokinetic analysis were obtained during Visits 4, 6 and 8 (or at discontinuation)

Safety: Safety was assessed using adverse events, clinical laboratory results, vital signs, physical examinations, and electrocardiograms (ECGs).

Bioanalytical Methods: Plasma samples were analyzed for plasma concentrations of oxycodone, naloxone and metabolites using a previously validated analytical method. The results of these analyses will be reported separately.

Statistical Methods:

Efficacy Analyses: The primary and secondary analyses of bowel function were performed using the Full Analysis population. Secondary analyses on analgesic efficacy were performed on the Per-Protocol population. The secondary analysis on the Pain Intensity Scale was repeated for the full analysis population and the primary analysis (on the BFI) was repeated for the Per-Protocol Population, as an exploratory analysis.

Statistical hypothesis tests (comparisons) were conducted at the two-sided 0.05 level of significance.

A mixed-model repeated measures (MMRM) analysis of the PACOI were carried out for Days 8, 15, and 29 as repeated measures. The last observation carried forward (LOCF) method for missing values with previous values under double-blind treatment were applied. Missing baseline values were replaced by the most recent value before the randomisation visit. The repeated measures analysis included terms for treatment, country and time as a categorical variable, and pre-randomisation PACOI at the end of the Run-in Period. Through a gate keeping strategy, this secondary analysis had statistical significance only if the primary analysis had statistical significance. Confidence Intervals (95%) for the difference between treatments means were displayed.

The PGIC was analyzed using an analysis of variance (ANOVA) with factors for treatment and country. The two treatments were compared for superiority, and 95% confidence intervals for the difference in means between treatments was displayed. Through a gate keeping strategy, this secondary analysis had statistical significance only if the primary analysis of the BFI and the secondary analysis of the PACOI both had statistical significance. Thus, the level of significance of this secondary analysis was formally preserved at 0.05.

A mixed-model repeated measures (MMRM) analysis of Pain Intensity Scale – Average Pain over the last 24 Hours, as assessed at each double-blind study visit (assessed with a 0-10 scale at study visits up to Day 90), was carried out. The LOCF method for missing values with previous values under double-blind treatment was applied. The repeated measures analysis included terms for treatment, time as a categorical variable, and pre-randomisation value (at the end of the Run-in Period). To estimate differences in analgesia response between treatment groups, means and confidence intervals (95%) were displayed.

Pharmacokinetic and/or Pharmacodynamic Analyses: Estimates of the population mean and population variability for oxycodone and naloxone pharmacokinetic (PK) parameters were derived using a nonlinear mixed effects model, i.e., a population PK approach, using up to 3 samples per subject. PK results are presented in a separate report.

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

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 baseline (Visit 3) bowel function was comparable between the two groups (mean (SD) of 61.0 (23.39) in the Oxycodone PR group and 61.8 (22.95) in the Oxycodone/Naloxone PR group) but after four weeks (by Visit 6) mean BFI had improved considerably in the Oxycodone/Naloxone PR group (34.9 (25.80)) and this reduction of 26.9 points in the BFI score was clinically relevant. In addition, throughout the first 4 weeks of the double-blind phase (Visit 3 to Visit 6) the difference between the mean BFI scores of the groups was statistically significant (Oxycodone/Naloxone PR vs Oxycodone PR, -15.2, $p<0.0001$; CI -18.2, -12.2) and clinically relevant in favour of the Oxycodone/Naloxone PR group at Visit 6 (51.6 (26.78) in the Oxycodone PR group vs 34.9 (25.80) in the Oxycodone/Naloxone PR group).

This improvement in mean BFI score in the Oxycodone/Naloxone PR group began to be evident just 1 week after randomisation and continued past the 4 week stage to the end of the study (Visit 8) at which time there was still a statistical and clinically relevant difference in BFI score between the groups in favour of the Oxycodone/Naloxone PR group (45.7 (29.88) in the Oxycodone PR group vs 31.1 (26.76) in the Oxycodone/Naloxone PR group) (Oxycodone/Naloxone PR vs Oxycodone PR, -14.6, $p<0.0001$; CI -20.7, -8.6)

Also, the improvement in mean BFI scores within the Oxycodone/Naloxone PR group, from a baseline of 61.8 (22.95), to the end of double-blind period value of 31.1 (26.76), is clinically relevant (a mean reduction of 30.7 points on the BFI score).

These results confirm the superiority of Oxycodone/Naloxone PR over Oxycodone PR based on primary analysis of the BFI.

After 4 weeks in the double-blind phase subjects in the Oxycodone/Naloxone PR group had a statistically significant improvement in symptoms of constipation compared to subjects in the Oxycodone PR group (-3.54; $p<0.0001$; CI, -4.56, -2.51 by Visit 6) as measured by the PACOI score. Again this difference between the groups was evident as early as Visit 4 and continued until Visit 8. By means of the pre-specified hierarchical test procedure, the BFI and PACOI improvement with Oxycodone/Naloxone PR vs Oxycodone PR could be shown confirmatorily.

Subjects in the Oxycodone/Naloxone 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 Oxycodone PR group (1.66; $p<0.0001$; CI, 1.33, 2.07). The difference was the equivalent of 1 extra 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 Oxycodone/Naloxone PR group compared to the Oxycodone PR group (for PAC-SYM, $p=0.0001$; CI -5.50, -2.83, by Visit 6). An improvement was noted in the Oxycodone/Naloxone 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, remained constant throughout the double-blind phase. These results, combined with the severity and interference of pain and 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 Oxycodone PR and Oxycodone/Naloxone PR.

The results of the extension phase of this study will be presented in a separate report (OXN3001S).

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

Safety: 102 Subjects (63.8%) experienced 305 incidences of adverse events in the Oxycodone PR group and 98 subjects (60.5%) experienced 292 incidences of adverse events in the Oxycodone/Naloxone PR group. As is expected with this class of drugs, the most common class of adverse events was gastrointestinal (a total of 79 subjects (24.5%) in the study experienced gastrointestinal adverse events). Nausea, diarrhoea and dizziness were the three most common adverse events in the Oxycodone PR group and nausea, diarrhoea and urinary tract infection were the three most common adverse events in the Oxycodone/Naloxone PR group.

There were fewer gastrointestinal adverse events in the Oxycodone/Naloxone PR group. Only 31 (19.1%) of subjects in the Oxycodone/Naloxone PR group experienced gastrointestinal adverse events compared to 47 (29.4%) of subjects in the Oxycodone PR group. The number of subjects experiencing diarrhoea was generally low, and incidences were transient in duration and comparable between groups.

A total of 13 subjects (9 in the Oxycodone PR group and 4 in the Oxycodone/Naloxone PR group) had serious adverse events and there were slightly more subjects that discontinued study medication due to adverse events in the Oxycodone PR group than in the Oxycodone/Naloxone PR group (15 subjects (9.4%) vs 7 subjects (4.3%) respectively).

2 Subjects had adverse events that were considered by the investigator to be related to opioid withdrawal, one in each treatment group. However, in general SOWS scores were stable, low and comparable between groups throughout the study, including during the switch to double-blind treatment. Clinical laboratory, vital sign, and ECG results showed nothing of potential clinical concern. However, ECG changes or signs and symptoms of cardiac arrhythmia will be part of continuous safety monitoring in the clinical development program as well as in post marketing routine pharmacovigilance activities.

Conclusions: This study provides evidence that Oxycodone/Naloxone PR is superior to Oxycodone PR 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 comparable in both groups. 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 Oxycodone/Naloxone PR group. Oxycodone/Naloxone PR showed no additional or unexpected risk compared to Oxycodone PR treatment. In consequence, a favourable benefit to risk ratio could be demonstrated for Oxycodone/Naloxone PR in this clinical study for the investigated indication.

Date of the Report: 05 October 2007