2. SYNOPSIS

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)	Referring to Part IV of the Dossier	
Name of Active Ingredient: Oxycodone/naloxone combination	Volume: Page:	

Title of the Study: A Randomised, Double-blind, Placebo- and Active-controlled, Double-dummy, Parallel Group Study to Determine the Safety and Efficacy of Oxycodone/Naloxone Prolonged-release Tablets in Subjects with Moderate to Severe, Chronic Nonmalignant Pain

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		

Publication (Reference): None

Study Dates:	**Study Status:**	**Phase of Development:**
19-Jan-2005 to 10-May-2006	Completed	Phase 3

Objectives: The primary objective was to demonstrate the superiority of OXN over placebo over time from the initial dose of study medication to multiple pain events (inadequate analgesia) during the Double-blind Phase.

Methodology: This was a double-blind, placebo- and active-controlled, double-dummy, parallel group, randomised, maintenance of analgesia study using oxycodone/naloxone (OXN), prolonged release oxycodone (OXY PR), or placebo to treat moderate to severe, chronic nonmalignant pain. This trial employed supplemental analgesic medication use.

Number of Subjects: Planned: 450 subjects. Randomised: 464 subjects, 463 received study medication (151 received OXY, 154 received OXN, 158 received placebo). Completed: 402 subjects (133 received OXY, 136 received OXN, 133 received placebo). Completed per protocol: 263 subjects (87 received OXY, 82 received OXN, 94 received placebo).

Caveat: Subjects from site No. 699 (31 enrolled, 24 randomised) were excluded from all populations and analyses. This was due to the non-GCP compliance of the site, as indicated by a BfArM site inspection. The exclusion of these data from the analyses was agreed with the BfArM (see teleconference minutes and letter to the BfArM in Study Master File).

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. Pain had to be adequately managed by an opioid analgesic for at least the past 2 weeks. Subjects currently taking the equivalent of < 10 mg/d or > 40 mg/d oxycodone were excluded.

Test Treatment, Dose, and Mode of Administration:
Run-in Period (Pre-randomisation Phase): oxycodone immediate-release capsules (OxyIR) 5 mg

Double-blind Phase: OXN 10/5 and 20/10 mg oxycodone/naloxone combination tablets and OXY-matched placebo tablets

Extension Phase: OXN 10/5, 20/10, and 40/20 mg oxycodone/naloxone combination tablets

Reference Treatment, Dose, and Mode of Administration:
Double-blind Phase: oxycodone prolonged-release tablets (OXY) 10 and 20 mg, OXN-matched and OXY-matched placebo tablets

Extension Phase: none

Duration of Treatment: Pre-randomisation Phase: up to 28 days. Double-blind Phase: 12 weeks. Extension Phase: up to 12 months.

Treatment Schedule:

Pre-randomisation Phase (up to 28 days)

Screening Period- Prospective Assessment (up to 7 days):

At Visit 1, after written informed consent was obtained, the subject underwent evaluation for study eligibility. Subjects meeting the Prospective Assessment Criteria could continue in the study.

Screening Period- Opioid Taper (up to 7 days):

At Visit 2, subjects began an opioid tapering regimen, which involved down-titrating the subjects' opioid medication. During this time, subjects with a Pain Intensity Scale Score ≥ 5 were permitted to take a dose of open-label OxyIR, prescribed q4-6h as needed (PRN) at a dose of 1/4 the total daily opioid medication dose. At Visit 3, subjects meeting the Run-in Period Entrance Criteria (ie, who demonstrated need for continued opioid treatment over 2 consecutive days within 7 days after initiation of the Opioid Taper and did not exhibit excessive signs or symptoms of opioid withdrawal) received oxycodone immediate-release capsules (OxyIR; OxyNorm® 5 mg) for 14 days during the Run-in Period.

Run-in Period (14 days):

OxyIR was titrated to establish an effective and tolerated analgesic dose. The target dose of OxyIR was 20 or 40 mg/d.

Double-blind Phase (12 weeks):

At Visit 4, subjects meeting Randomisation Criteria (ie, who tolerated and achieved adequate analgesia with 15-40 mg/d OxyIR; *acc. to Amendment 2, dated 25 May 2005: 15-45 mg/d OxyIR*) were randomised to OXN, OXY or placebo (1:1:1). Subjects were converted from the effective dose of OxyIR to a fixed, symmetrical dose of the double-blind study medication (ie, OXN, OXY, or placebo). Subjects with a Pain Intensity Scale Score ≥ 5 were permitted to take a dose of open-label OxyIR, prescribed q4-6h PRN at a dose of 1/4 the total daily opioid medication dose. Visits 5-8 occurred at Weeks 2, 4, 8, and at week 12, at the end of study or upon early discontinuation.

Extension Phase (up to 52 additional weeks):

At Visit 8b, subjects meeting the Extension Phase Entrance Criteria (ie, completed the Double-blind Phase) had the option to receive open-label OXN for up to 12 additional months during the Extension Phase. All subjects were switched to 20/10 mg/d oxycodone/naloxone. Dose titration was permitted at the discretion of the Investigator.

Criteria for Evaluation:

Analysis Populations: **Enrolled:** provided informed consent; **Opioid Taper Safety:** entered the Opioid Taper and then assessed for safety; subjects who skipped the Opioid Taper were also included; **Run-In Safety:** dosed in the Run-in Period and then assessed for safety; **Double-Blind Safety:** dosed during Double-blind Phase and then assessed for safety; **Full Analysis:** randomised, dosed, and then assessed for efficacy; double-blind safety and full analysis populations were based on the randomised treatment; **Per Protocol:** sufficiently complied with the protocol (as defined prior to unblinding); **Caveat:** Data from site No. 699 were excluded from all populations and analyses (see above).

Efficacy: The primary efficacy variable (defined in Objectives above) was composed of the following:

- Pain Intensity Scale (0-10) "Average Pain over 24 hours" score obtained each evening.
- Pain Intensity Scale (0-10) "Pain Right Now" score obtained whenever the pain reached ≥ 5.
- Rescue medication use.

Other assessments included bowel function and the modified Brief Pain Inventory- Short Form (modified BPI-SF).

Pharmacokinetics (PK): Population pharmacokinetics were investigated. PK results are reported in a separate report.

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

Statistical Methods:

Efficacy Analyses: The primary efficacy variable, time to multiple (ie, recurring) pain events (inadequate analgesia), was analysed using the approach of Wei, Lin, and Weissfeld[11], which employed a marginal Cox proportional hazards regression. The primary comparison was a superiority analysis between OXN and placebo, at the two-sided 5 % level of significance.

A pain event was demonstrated by unacceptable pain control for 2 consecutive days. Each pain event was 2 discrete days, eg, there could be a maximum of 2 pain events in 4 days. A day of unacceptable pain control was defined as:

1) Pain Intensity Scale ("Average Pain over 24 Hours") score ≥ 5 or
2) Pain Intensity Scale (" Pain Right Now") score ≥ 5 accompanied by rescue medication dosing ≥ 2 times over one day OR
3) Subjects could have a pain event by study discontinuation due to lack of therapeutic effect.

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

Results:

Efficacy: For the full analysis population, the appearance of pain events was significantly rarer under oxycodone/naloxone compared to placebo, reducing the risk of pain events to 58% ($p<0.0001$). The appearance of pain events was comparable for oxycodone/naloxone versus oxycodone, increasing the risk of pain events by 6% ($p=0.69$). The results in the per protocol population were comparable.

The evidence seen in the primary analysis is further confirmed by the statistically significant treatment differences seen in the analysis of the 24-hour average pain values ($p=0.0396$), BPI-SF pain subscores ($p=0.0158$), OXYIR intake ($p=0.0004$) and BPI-SF sleep interference scores ($p=0.0030$).

The PGIC and BPI-SF interference subscores showed lower (better) values with oxycodone/naloxone compared to placebo. The differences between the oxycodone/naloxone and the placebo group tended towards statistical significance (PGIC $p=0.07$; BPI-SF interference $p=0.09$).

The results of the BFI scores and number of CSBMs showed a significant improvement in bowel function with oxycodone/naloxone treatment compared to oxycodone treatment (BFI $p=0.03$; CSBM1 Odds ratio=2.2, CSBM3 Odds ratio=1.7).

Safety: There were no significant changes in clinical laboratory tests, vital signs and ECG results during the study.

The incidence of treatment-emergent adverse events was comparable between the oxycodone/naloxone, oxycodone and placebo treatment group. The most frequently reported treatment emergent adverse events were constipation, nausea, headache, vomiting and diarrhea. Theses AEs are consistent with the expected adverse event profile of the opioid analgesic class of drugs.

In the oxycodone/naloxone group, SAEs in only two subjects were assessed as being possibly related to study drug by the investigator and SAEs in only three subjects were assessed as being possibly related to study drug by the sponsor.

Conclusions: This study provides evidence that oxycodone/naloxone is superior to placebo with regards to pain relief. 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. With oxycodone/naloxone treatment bowel function is significantly improved compared to oxycodone treatment. No apparent safety concerns of treatment with oxycodone/naloxone were identified. Importantly, adverse events and SOWS sumscores were not exacerbated by the addition of naloxone to oxycodone therapy. Due to the low number of subjects that experienced possibly related SAEs, oxycodone/naloxone showed no additional risk compared to oxycodone treatment.

Date of the Report: 12-July-2007