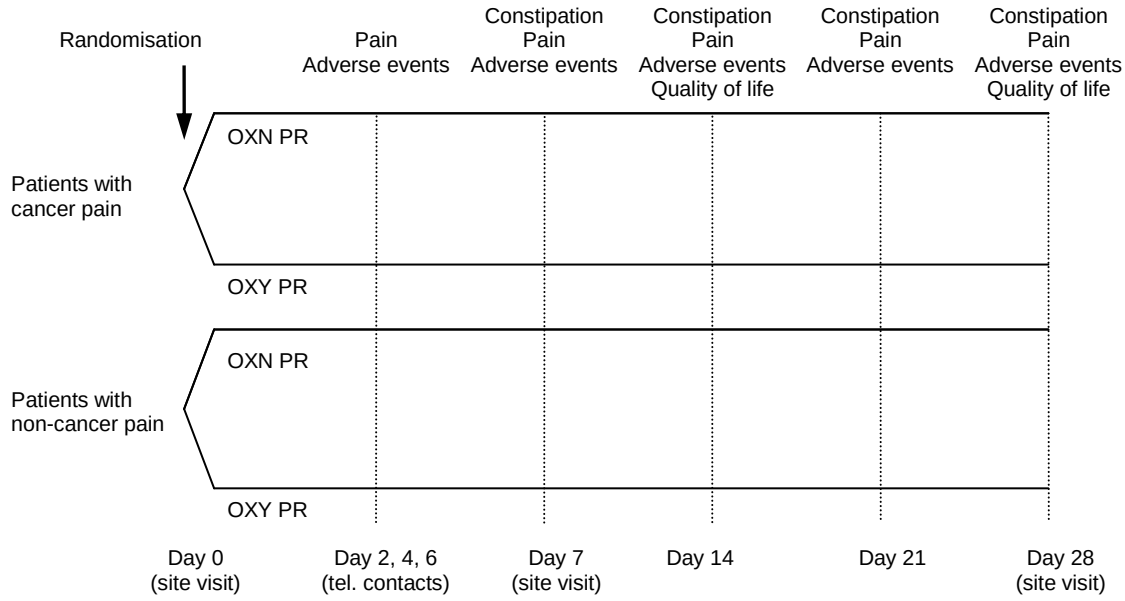
2. SYNOPSIS

<table>
<tr><td>Name of Sponsor:
Mundipharma SAS</td><td>INDIVIDUAL STUDY TABLE</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Name of Finished Product:
Oxycodone/naloxone 5 mg/2.5 mg, 10 mg/5 mg, 20 mg/10 mg, and 40 mg/20 mg prolonged release tablets</td><td rowspan="2">Referring to Part … of the Dossier

Volume: Page:</td></tr>
<tr><td>Name of Active Ingredient:
Oxycodone/naloxone combination</td></tr>
<tr><td colspan="2">Protocol No.: OXN3505</td><td>EudraCT/IND No.: 2009-012051-20</td></tr>
<tr><td colspan="3">Title of the Study: Study of the efficacy of prolonged release oxycodone/naloxone (OXN PR), compared to prolonged release oxycodone (OXY PR), for the reduction of the intensity of opioid-induced constipation symptoms in patients treated for cancer or non-cancer pain: A randomised, double-blind, controlled, multicentre study.</td></tr>
<tr><td colspan="3">Investigators: 82 centres in France.</td></tr>
<tr><td colspan="3">Publication (Reference): None.</td></tr>
<tr><td>Study Dates:
11-Feb-2010 to 28-Jun-2011</td><td>Study Status:
Completed</td><td>Phase of Development:
Phase 3</td></tr>
<tr><td colspan="3">Objectives:<u>Primary objective:</u>
• To study the efficacy of OXN PR, compared to OXY PR, for the reduction of the intensity of opioid-induced constipation symptoms in patients treated for cancer or non-cancer pain.
<u>Secondary objectives:</u>
• To verify that OXN PR is non-inferior to OXY PR for pain control in these patients.
• To further document overall OXN PR safety.
• To evaluate compliance to OXN PR treatment versus OXY PR treatment.
• To evaluate gastrointestinal-related quality of life in patients treated with OXN PR or OXY PR.</td></tr>
<tr><td colspan="3">Methodology:Multicentre, national, randomised (1:1), double-blind, double dummy, controlled (OXN PR vs. OXY PR), parallel group, 4-week trial stratified on the cause of pain: cancer or non-cancer.
The study included one inclusion/randomisation visit on Day 0, three telephone contacts on Days 2, 4, and 6 to assess the need of study drug titration, one follow-up visit on Day 7, and one end-of-study visit on Day 28. Patients completed a diary each week. Bowel function, use of laxatives, pain intensity, treatments received and adverse events were assessed on Days 0, 7, 14, 21 and 28. Gastrointestinal-related quality of life was evaluated on Days 0, 14 and 28.
Any patient having completed this core study and wishing to receive OXN PR afterwards could enter an optional open extension phase. During this phase, all patients received OXN PR and were managed as per the usual practice in the centre until commercial OXN PR is available in France (or until 31 October 2012 at the latest). Adverse events were assessed at each visit.
The present report refers only to the core study.</td></tr>
</table>

Study Design Graphic:



Number of Patients:

- Planned: 624 patients overall: 312 with cancer pain and 312 patients with non-cancer pain.
- Randomised: 225 patients: 114 to the OXY PR group and 111 to the OXN PR group
- Completed: 181 (80.4%) patients completed the core study and 44 (19.6%) withdrew prematurely: 21.1% in the OXY PR group and 18.0% in the OXN PR group (p=0.566).
- Analysed: 207/225 (92.0%) randomised patients were included in the ITT population: 106 in the OXY PR group and 101 in the OXN PR group. 167/225 (74.2%) randomised patients were included in the PP population: 85 in the OXY PR group and 82 in the OXN PR group. All 225 randomised patients were included in the Safety population.

Indication and Criteria for Inclusion:

Male or female adult patients with documented cancer or non-cancer pain, either currently receiving a WHO step II opioid and requiring the initiation of a WHO step III opioid (due to a lack of efficacy of the step II opioid) expected to last 28 days or more, or currently receiving a WHO step III opioid expected to last further 28 days or more, and having opioid-related constipation defined by either a KESS score ≥9 or the current use of laxatives (≥3 times per week).

Test Treatment, Dose, and Mode of Administration:

- Oxycodone/naloxone prolonged release (OXN PR), 5 mg/2.5 mg, 10 mg/5 mg, 20 mg/10 mg, and 40 mg/20 mg tablets, for q12h oral administration. Batch numbers: PN3331, PN3390, PN3343, PN3487, PN3388, PN3506.
- Matching placebo for oxycodone prolonged release (OXY PR), 5 mg, 10 mg, 20 mg, and 40 mg tablets, for q12h oral administration. Batch numbers: PN3423 (=PN3221), PN3217, PN3218, PN3219.

Reference Treatment, Dose, and Mode of Administration:

- Oxycodone prolonged release (OXY PR), 5 mg, 10 mg, 20 mg, and 40 mg tablets for q12h oral administration. Batch numbers: PN3352, PN3355, PN3354, PN3367.
- Matching placebo for oxycodone/naloxone prolonged release (OXN PR), 5 mg/2.5 mg, 10 mg/5 mg, 20 mg/10 mg, and 40 mg/20 mg tablets, for q12h oral administration. Batch numbers: PN3226, PN3228, PN3229, PN3230, PN3491.

Concomitant Medication Including Rescue:

- Patients already taking non-opioid analgesics and all other concomitant medications (including those for the treatment of depression) are eligible to take part in the study. However, all concomitant medications that were considered necessary for the patient's welfare could be continued at a stable dose throughout the study and under the supervision of the Investigator.
- Rescue analgesic therapy: Oxycodone immediate release (Oxy IR), 5 mg capsules for q4-6h oral

administration. Batch number PN3502. Use at the discretion of the Investigator, in accordance with the SPC.

- Rescue laxative medication: Bisacodyl, 5 mg tablets. Batch number PN3500 (Ducolax®, Boehringer Ingelheim). On the day of randomisation pre-study laxatives were discontinued. If no bowel movement occurred within 3 days after randomisation, only bisacodyl oral intake was started as a rescue laxative. Investigators instructed their patients that if they exhibited discomfort during the 3-day period they could take oral bisacodyl as a laxative earlier than 3 days after their most recent bowel movement. The maximum allowed number of bisacodyl intakes was 5 dosages within 7 consecutive days.

Duration of Treatment:

- Planned duration of treatment: 28 days in the core study.
- Study duration: 28 days per patient, 16-month inclusion period, thus 17 months in total.

Treatment Schedule: Daily dose ranging from 20 mg/10 mg to 160 mg/80 mg oxycodone/naloxone (20, 30, 40, 60, 80, 100, 120, 140 and 160 mg oxycodone) or 20 mg to 160 mg oxycodone (20, 30, 40, 60, 80, 100, 120, 140 and 160 mg), at the discretion of the Investigator, in accordance with the Summary of Product Characteristics (SPC), during 28 days.

Criteria for Evaluation:

Primary Efficacy Criterion

- Change of intensity of constipation symptoms, as assessed by the Bowel Function Index (BFI) from baseline to Day 28.

  The BFI is the mean value of 3 single items: 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 judgement of constipation (NAS, 0=not at all, 100=very strong).

Secondary Efficacy Criteria

- Change of Bowel Function Index (BFI) from baseline to Days 7, 14 and 21.
- Change of Patient Assessment of Constipation Symptoms (PAC-SYM) score from baseline to Days 7, 14, 21 and 28.
- Change of Knowles Eccersley Scott Symptom (KESS) score from baseline to Days 7, 14, 21 and 28.
- Frequency of laxative medication use between Day 0 and Day 28.
- Change of pain as assessed by the Brief Pain Inventory-Short Form (BPI-SF) score from baseline to Days 7, 14, 21 and 28.
- Frequency of rescue medication use between Day 0 and Day 28.
- Persistence with the assigned treatment on Day 28.
- Number of prescribed doses missed between Day 0 and Day 28.
- Change of Gastrointestinal Quality of Life Index (GIQLI) score from baseline to Days 14 and 28.

Safety Criteria

- Adverse events from baseline to Day 28.
- Clinical laboratory results on Day 28.
- Vital signs and physical examination on Days 7 and 28.
- 12-lead electrocardiogram on Day 28.

Statistical Methods:

All analyses were stratified on the type of pain and all tests were performed at the α=0.05 significance threshold.

Analysis Populations: Intent-to-treat (ITT) population: all randomised patients with at least one efficacy assessment (BFI data on Day 0 and BFI data at another visit).

- Per protocol (PP) population: all patients having received at least one dose of the study medication, with no major violation of the study protocol. Violations were defined during a final review of the study data, before unblinding.
- Safety population: all patients having received at least one dose of study medication.

Primary Efficacy Analysis:

Treatment groups were compared for the mean change of BFI from baseline to Day 28 using the Student's t-test if data are normally distributed or Wilcoxon test if the data are not normally distributed.

Sensitivity analysis was performed on the ITT and PP, using the mixed-effects model for repeated measures (MMRM) including baseline BFI score as a covariate, and visit, treatment groups and treatment*visit interaction as factors. If interaction is significant, the comparison of interest is between

treatment groups at Day 28.

Secondary Efficacy Analyses:

Treatment groups were compared for the mean change of BFI from baseline to Day 7, Day 14, and Day 21 using the Student's t-test (normal distribution) or Wilcoxon test (non normal distribution).

Treatment groups were compared for the percentages of clinically responders from baseline to Day 7, Day 14, Day 21, Day and Day 28 (patient with a clinically meaningful change of BFI ≥12 from baseline to Day 7, Day 14, Day 21, Day and Day 28) and for the percentages of normalised patients from baseline to Day 7, Day 14, Day 21, Day and Day 28 (patient with BFI >28.8 at baseline and with BFI ≤28.8 on Day 7, Day 14, Day 21, Day and Day 28) using the Pearson's Chi square test or Fisher exact test.

Treatment groups were compared for the mean change of PAC-SYM and KESS scores from baseline to Day 7, Day 14, Day 21, and Day 28 using the Student's t-test (normal distribution) or Wilcoxon test (non normal distribution). For the KESS, treatment groups were compared for the percentages of patient with KESS score ≥9 at baseline and with KESS score <9 on Day 7, Day 14, Day 21, and Day 28 using the Pearson's Chi square test or Fisher exact test.

The non inferiority of OXN PR to OXY PR for pain control was assessed by computing the one-sided 95% confidence interval (CI) of the BPI-SF score (pain subscale score and pain on the average score) on Days 14 and 28.

Treatment groups were compared for the GIQLI scores on Days 14 and 28 and for the mean change of GIQLI scores from baseline to Day 14 and Day 28 using the Student's t-test or Wilcoxon test.

Descriptive statistics were provided for all criteria. BFI and BPI analyses were performed in the ITT and PP populations; other analyses were performed in the ITT population.

Interim Analyses: N/A.

Safety Analyses:

Study medication (OXN PR, OXY PR, rescue analgesics, and rescue laxative) was summarised in the safety population. Treatment exposure was defined as the number of days on study medication. This was calculated as the number of days between the first and last dose of study medication.

Treatment exposure was summarised by treatment group for the titrated dose level. Treatment discontinuation data was summarised by treatment group as continuous or categorical data, as applicable. The number and percentage of patients exposed to study medication for overlapping time intervals (i.e. any exposure, ≥ 1 week, ≥ 2 weeks) was calculated by treatment group. The length of exposure (in days) to, the total intake of, and the average daily dose of each treatment were summarised by treatment group as continuous data. For each treatment group, a shift table was provided to show the number of patients in categories defined by the initial dose level and the maximum dose level reached.

For rescue Oxy IR, the number of 5 mg capsules and number of days with rescue medication intake during the study and average number of times per day that rescue medication was used during study was also summarised by treatment group of PR medication initial dose at randomisation (0 to ≤20, 20 to ≤40, 40 to ≤60, 60 to ≤80, and >80 mg).

Rescue analgesic medication and laxative intake were analysed using the Wilcoxon Rank Sum test.

Treatment groups were compared for the percentages of patients having stopped the assigned treatment before Day 28 or having missed 20% or more of the prescribed doses using the Pearson's Chi square test or Fisher exact test.

AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA TM) coding system to give a System Organ Class (SOC) and preferred term (PT) for each event. An overall summary of AEs was provided, by treatment group, for both the number and percentage of patients experiencing AEs, and the number of AEs reported. The number and percentage of patients reporting any AE was summarised by PT/SOC. In addition, the number of reported AEs was summarised. AEs were summarised by worst severity, relationship to study medication, action taken on study medication, and outcome. In addition, severe AEs, AEs leading to death, serious AEs, AEs leading to discontinuation from study, AEs requiring additional therapy, AEs leading to dose modification, and AEs leading to dose interruption were summarised.

Comparisons were done by treatment group and within each treatment group by age class (≤65 years, >65 years), using the Student's test or Wilcoxon test for continuous variables and Chi2 test or Fisher's exact test for categorical variables. The trend test was used with ordinal variables.

Laboratory results were classified using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.02. The number of patients with ≥1 abnormal result during the study was summarised using descriptive statistics for all parameters by treatment group. The incidence of abnormal (CTCAE grades) values was also provided by treatment group. Treatment groups were compared using the Student t-test or Wilcoxon test for continuous variables and Chi2 test or Fisher's exact test for categorical variables.

Vital signs, ECG results and physical examination findings were summarised descriptively by treatment group by visit. Treatment groups were compared using the Student t-test or Wilcoxon test for continuous variables and Chi2 test or Fisher's exact test for categorical variables.

Sample Size Rationale:

Assumptions:

- The analysis will be stratified on pain type.
- Tests will be performed at the α=0.05 significance threshold with a power (1 – β) ≥0.95, thus the overall power, for the primary efficacy analysis in both strata, will be 0.9025.
- The standard deviation of the ΔBFI will be ≤28.
- The minimal clinically relevant difference in BFI is 12.
- The randomisation ratio will be 1:1.

Under these assumptions the required number of patients was 142 in each treatment group. Assuming an early drop-out rate of 10%, 312 patients (2 x 156) were required in each pain type stratum and 624 patients were required overall.

Results:

As the rate of patient recruitment was low and despite the recruitment period was extended, recruitment had to be stopped before reaching a sample size sufficient to perform all the planned analyses.

Efficacy:

In the overall population, all BFI analyses at Day 28 showed no differences between the OXY PR and OXN PR groups in the overall population. In particular, although the change of BFI from baseline to Day 28 was -23.2 in average (median -26.7) in the OXN PR group and -18.2 in average (median -15.0) in the OXY PR group, the difference between treatment groups was not statistically significant (p=0.341, primary efficacy criterion).

The proportion of patients with clinically meaningful improvement (BFI improvement ≥12 points), i.e. the rate of clinically responders, was improved by 25.1% by using OXN PR compared to OXY PR. However, the difference between groups for proportion of patients with clinically meaningful improvement did not reach statistical significance: 65.2% in the OXN PR group and 52.1% in the OXY PR group (p=0.071).

The rate of normalised patients was improved by 26.5% by using OXN PR compared to OXY PR. However, there was also a non statistically significant difference for the rate of normalised patients: 38.2% in the OXN PR group and 30.2% in the OXY PR group (p=0.252).

There were no consistent significant differences between the OXY PR and OXN PR groups at any time point during the study for the BFI, the KESS, and the PAC-SYM scores (secondary efficacy criteria), which assess various aspects of the gastrointestinal function.

The results of BPI-SF (secondary efficacy criteria) showed globally that OXN PR was non-inferior to OXY PR for pain management.

There were no significant differences between the OXY PR and OXN PR groups for the GIQLI (secondary efficacy criteria), which assesses the health-related quality of life in patients with gastrointestinal disorders.

In patients with cancer pain, patients with non-cancer pain, and patients with neuropathic pain, there were also no consistent differences between the OXY PR and OXN PR groups whatever the variable.

Results of the comparison of OXY PR with laxative vs. OXN PR without laxative (although BFI results were in favour of OXN PR at Day 28) should not be interpreted for the BFI and the KESS, as significant difference between groups were observed at baseline. There were no consistent significant differences between OXY PR with laxative vs. OXN PR without laxative for the BPI-SF and the PAC-SYM.

Similar results were obtained in the ITT and PP populations.

Safety:

Overall, two thirds (66.1%) of patients received study medication for ≥4 weeks, and 46 (20.8%) patients discontinued the study medication during the study, either temporarily (n=6) or permanently (n=40). Mean exposure was 24.9 ± 8.66 days, with a mean total dose of 1213 ± 887 mg oxycodone and a mean daily dose of 49.9 ± 30.3 mg oxycodone.

Only 22/225 (9.8%) patients received >80 mg/day oxycodone, but this was due to the late date of the protocol amendment that authorised the investigators to include patients requiring doses higher than 80 mg/day oxycodone.

There were no significant differences between the OXY PR and the OXN PR groups for exposure to study medication and for the rate of patients who discontinued the study medication.

During the first two weeks of treatment, rescue Oxy IR was more frequently used in the OXN PR group. In addition, during the first week of treatment, rescue laxatives were used more frequently in the OXY PR

group. Afterwards, there were no further significant differences between treatment groups. These differences were seen in patients with ≤80 mg/day oxycodone but not in those with higher doses. However, the sample size in the subgroup with high doses was limited.

Overall, 52.9% of patients in the Safety population, 49.7% of patients aged ≤65 years and 64.0% of those aged >65 years, 52.7% of patients who received ≤80 mg/day oxycodone and 54.5% of those who received >80 mg/day oxycodone experienced at least one AE.

The incidence of AEs related to study medication was 40.9% overall, 42.9% in patients aged ≤65 years and 34.0% in those aged >65 years, 42.4% in patients with ≤80 mg/day oxycodone and 27.3% in those with >80 mg/day oxycodone.

AEs were similar in nature in both treatment groups. In addition, there were no significant differences between the OXY PR group and the OXN PR group for the incidence of AEs, SAEs and deaths either overall, in age subgroups or in dose subgroups. There were also no marked differences between treatment groups when considering AEs and SAEs related to study medication.

Five deaths occurred during the study, but none was related to the study medication.

Three patients experienced SAEs considered as related to study medication: 1 (0.9%) in the OXY PR group and 2 (1.8%) in the OXN PR group. The following SAEs were declared as SUSARs: unlikely related arterial occlusive disease, myocardial infarction and myocardial ischaemia in one patient in the OXY PR group; and possibly related urinary retention, renal failure, faecaloma, eschar and dehydration in one patient in the OXN PR group.

All other AEs that occurred during the study had already been described with the study medications.

Clinical laboratory evaluations, vital signs, ECG and physical examination raised no safety concerns.

Therefore, OXY PR and OXN PR showed similar safety profiles in this study. A good safety profile was observed with both products at doses higher than 80 mg/day oxycodone and in patients aged above 65 years.

Conclusions:

In this French population of patients with cancer pain and non-cancer pain, the observed differences of efficacy between OXY PR and OXN PR for the reduction of the intensity of opioid-induced constipation symptoms were not statistically significant.

The improvements obtained with OXN PR in this study are however in line with those of previous OXN PR studies. Therefore, the lack of statistically significant difference vs. OXY PR is likely due to the unexpectedly large and rapid improvement obtained with OXY PR in this study, by contrast with previous studies. Other possible explanations include the use of different evaluation criteria and assessment tools, as well as the limited sample size.

OXN PR was non-inferior to OXY PR for the reduction of pain intensity, as shown in previous studies.

OXY PR and OXN PR showed similar safety profiles in this study, as shown in previous studies. In addition, we observed a good safety profile of both products at doses higher than 80 mg/day oxycodone and in patients aged above 65 years.

Date of the Report: 22-Mar-2013