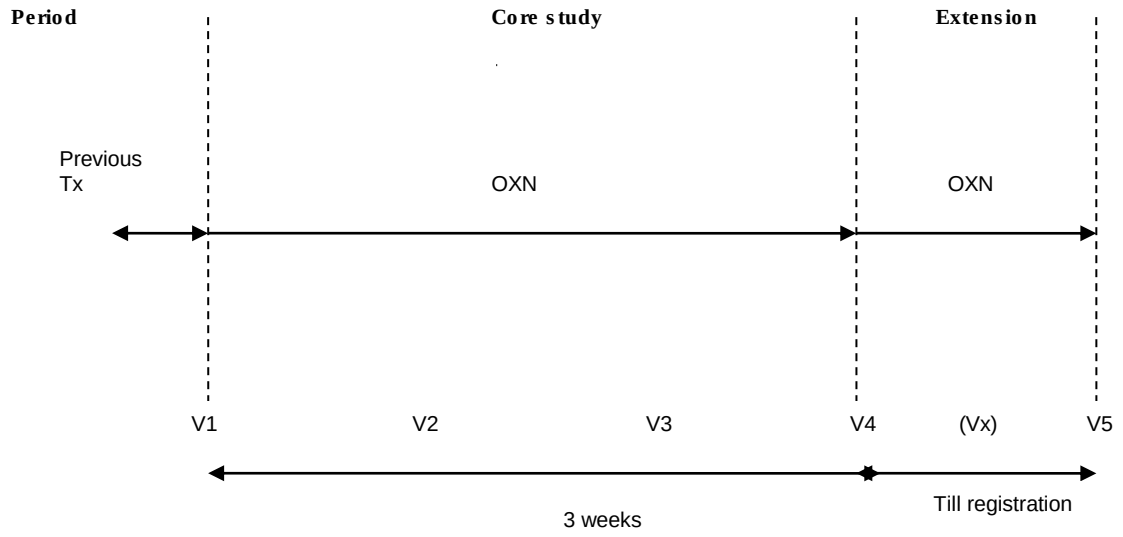
2. SYNOPSIS

<table>
<tr><td>Name of Sponsor:
Mundipharma Pharmaceuticals BV</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)</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.: OXN3501</td><td>EudraCT/IND No.: 2008-001026-14</td></tr>
<tr><td colspan="3">Title of the Study: An open study with OXN to evaluate the patient preference for pain treatment with respect to quality of life after WHO step I or step II analgesics for patients with moderate to severe non-malignant pain</td></tr>
<tr><td colspan="3">Investigators: This study was conducted at a total of 20 sites in 2 countries (9 in Belgium and 11 in The Netherlands).</td></tr>
<tr><td colspan="3">Publication (Reference): van Dongen VC et al. Patient preference with respect to QoL and reduction in opioid-induced constipation (OIC) after treatment with prolonged-release (PR) oxycodone/naloxone compared with previous analgesic therapy (PREFER study). Int J Clin Pract May 23. Doi:10.1111/icjp.12468. (ePub ahead of publication).</td></tr>
<tr><td>Study Dates:
02-Jun-2009 to 23-Jan-2012</td><td>Study Status:
Completed</td><td>Phase of Development:
Phase 3B</td></tr>
<tr><td colspan="3">Objectives: The primary objective of this study was to determine the subject preference of OXN treatment compared to previous WHO step I or II analgesics with respect to quality of life (5 categories). The secondary objectives of this study were:
- To evaluate subject preference of OXN compared to previous WHO step I or II analgesics with respect to overall treatment (5 categories)
- To assess symptoms of constipation [Bowel Function Index (BFI), 2 questions and laxative use]
- To evaluate pain relief (NAS, 0-100)
- To assess safety of OXN treatment
- To assess the Quality of Life [EuroQuol (EQ-5D questionnaire)]</td></tr>
<tr><td colspan="3">Methodology: This was a multi-centre, open-label study in subjects with moderate to severe non-malignant pain, conducted to determine subject's preference of OXN treatment compared to previous WHO step I or II analgesics with respect to quality of life. Subjects received OXN for 3 weeks in the core study. When subjects participated in the extension phase of the study, they received OXN until registration of OXN in The Netherlands or Belgium or until discontinuation on request of the subject.</td></tr>
</table>

Study Design Graphic:



Number of Subjects: It was planned to include 215 subjects in order to obtain a total of 180 evaluable subjects with moderate to severe non malignant pain. In total, 169 subjects participated in this study. They were devided by WHO Step (n = 56 in WHO Step 1 group, n = 106 in WHO Step 2 group, n = 7 others) as well as by constipation (n = 105 with BFI < 28.8 and n = 64 with BFI ≥ 28.8). In the extension phase, 76 subjects were included: n = 22 in WHO Step 1 group, n = 51 in WHO Step 2 group, n = 3 others; n = 41 with BFI < 28.8 and n = 35 with BFI ≥ 28.8.

Indication and Criteria for Inclusion: Male or female subjects at least 18 years or older with moderate to severe non-malignant pain treated with WHO step I or II analgesics with insufficient pain relief and/or unacceptable side effects that required around-the-clock opioid therapy (starting dose of oxycodone over 20 mg/day) and were likely to benefit from WHO step III opioid therapy for the duration of the study.

Test Treatment, Dose, and Mode of Administration:

The starting dose of OXN for each subject was 10/5 mg twice a day. During the core study, the study medication was titrated with 5/2.5 mg OXN, or higher doses, to a maximum of 120 mg per day of oxycodone.

	Study medication	**Study medication**	**Study medication**
Dosage form	Oral (Tablets)	Oral (Tablets)	Oral (Tablets)
Unit strength	5/2.5 mg oxycodone / naloxone combination	10/5 mg oxycodone / naloxone combination	20/10 mg oxycodone / naloxone combination
Manufacturer	Mundipharma	Mundipharma	Mundipharma
Product code	BEOXN0525, NLOXN0525	BEOXN1005, NLOXN1005	BEOXN2010, NLOXN2010
Batch/Lot number	PN3331(140317), 150514	PN3351(142741), 147366, 148185	PN3343(142742), 147368, 148099
Date of manufacture	Feb-2008, Jun-2009	Jul-2008, Oct-2008, Jan-2009	Jul-2008, Dec-2008, Jan-2009
Expiration date	Feb-2011, Jun-2011	Jul-2011, Oct-2011, Jan-2012	Jul-2011, Dec-2011, Jan-2012

	Study medication	**Rescue medication**
Dosage form	Oral (Tablets)	Oral (Capsules)
Unit strength	40/20 mg oxycodone / naloxone combination	5, 10, 20 mg oxycodone
Manufacturer	Mundipharma	Mundipharma
Product code	BEOXN4020, NLOXN4020	OXN3501-oxy5, OXN3501-oxy10, OXN3501-oxy20 OXN3504-oxy5, OXN3504-oxy10, OXN3504-oxy20
Batch/Lot number	PN3282(138134), 150511	142816, 146804 (5 mg) 142818, 145925, 146514 (10 mg) 141920, 145923 (20 mg)
Date of manufacture	Sep-2007, May-2009	Jun-2008, Jul-2008, Oct-2008, May-2008
Expiration date	Sep-2010, May-2012	Jun-2011, Nov-2011 (5 mg) Jul-2011, Oct-2011, Dec-2011 (10 mg) May-2011, Oct-2011 (20 mg)

Reference Treatment, Dose, and Mode of Administration: No reference treatment.

Concomitant Medication Including Rescue: The use of the laxatives movicolon, bisacodyl or lactulose was allowed as well as the use of antidiarrhoeals. Open label oxycodone immediate release capsules was made available as rescue medication.

Duration of Treatment: Subjects received OXN for 3 weeks in the core study. When subjects participated in the extension phase of the study, they received OXN until registration of OXN in The Netherlands or Belgium or until discontinuation on request of the subject.

Treatment Schedule: The starting dose of OXN was 10/5 mg twice a day. The study medication was titrated with 5/2.5 mg OXN, or higher doses, to a maximum of 120 mg per day of oxycodone.

Criteria for Evaluation:

Efficacy Assessments:

Primary Efficacy Variable

The subject preference of OXN compared to previous WHO step I or II analgesic therapy with respect to quality of life, at any time during treatment was measured.with a 5 points ordinal scale. For the analysis, the ordinal scale was reduced to a binary scale: responder (score 4 or more) or no responder (score below 4).

Seconday Efficacy Variables

The subject preference of OXN compared to previous WHO step I or II analgesic therapy with respect to overall treatment, at any time during treatment was measured on a 5 points ordinal scale. For the analysis, the ordinal scale was reduced to a binary scale: responder (score 4 or more) or no responder (score below 4). Quality of Life was assessed by subjects by completing the EuroQol EQ-5D questionnaire at Visits 1 and 4 during the core study and at Visit 5 in the extension phase. Bowel Function Index was assessed for each subject. Laxative medication use and rescue medication use was recorded throughout the study. Pain was recorded on a numeric analogue scale (0-100) at each visit during the core study and the final visit in the extension phase. The number of bowel movements 7 days before the study visit and the number of days with a bowel movement in the last 7 days before the study visit were recorded.

Safety: Safety assessments consisted of monitoring and recording all adverse events (AEs) and serious adverse events (SAEs).

Statistical Methods:

Analysis Populations:

The enrolled population was defined as all subjects who provided written informed consent. The full analysis population (FAP) was defined as all subjects who received at least one dose of study medication and who had at least one post-baseline evaluation. The per-protocol population (PPP) was defined as all subjects who received at least one dose of study medication without major protocol violations. Major protocol violations were agreed prior to database lock. The safety population was defined as all subjects who received at least one dose of study medication and who had at least one safety assessment after that dose. The extension safety population was defined as all subjects who received at least one dose of study medication during the extension study and who had at least one post-dose evaluation during the extension study.

Efficacy Analyses:

Primary efficacy variable:

The subject preference of OXN compared to previous WHO step I or II analgesic therapy with respect to quality of life at Visit 2, Visit 3 and Visit 4 was listed, summarised and graphed by previous used analgesic group as a 5-points response. If a subject scored a better or much better at any time during the core study, this patient was a 'responder'. Response rates, overall and for each previous used analgesic group, were presented with 95% confidence intervals. The difference in response rates between both previous used analgesic groups with 95% confidence interval is presented. The Fisher's exact test was used to test if the response rate is dependent of previous used analgesic group. Explorative univariate and multivariate logistic regression analysis was used to search for possible prognostic variables, as age, sex, pain diagnosis, BFI at baseline, predicting the response in patient preference of OXN compared to previous analgesic therapy with respect to quality of life response rate. In the stepwise multivariate logistic regression analysis an entry criterion of 0.20 and a stay criterion of 0.05 was used.

Secondary efficacy variable:

- Pain NAS scores at each visit and absolute changes in pain NAS scores with 95% confidence intervals were summarised by visit, overall and by previous used analgesic group. At each visit, the paired t-test or Wilcoxon signed rank test was used to test if the change from baseline was statistically significant different from 0. At Visit 4, ANCOVA analyses were used to test if there was a difference in changes from baseline between both previous used analgesic groups. Previous used analgesic group, constipation group, interaction between previous used analgesic group and constipation group and baseline pain NAS scores were used as covariates in this analysis.
- The three items of the Bowel Function Index as the calculated BFI and the absolute change from baseline in BFI were summarised by visit, overall and by previous used analgesic group. The BFI and BFI sub scores were analyzed as the Pain NAS score. ANCOVA analyses were performed for the BFI score. Previous used analgesic group, constipation group, interaction between previous used analgesic group and constipation group, and baseline BFI were used as covariates in this analysis.
- The number of bowel movements in the last 7 days and the number of days with a bowel movement in the last 7 days were summarised by visit, overall and by previous used analgesic group. The results were displayed graphically.
- The use of laxatives previous to and during the study were listed with start and end date, and with dose. The percentage of subjects using laxatives previous to Visit 1 and previous to each visit, the number of subjects using laxatives during the study, and the duration of laxative use during the study were summarised overall and by previous used analgesic group.
- If immediate release for severe pain was necessary, open label oxycodone immediate release capsules was made available to patients as rescue medication. The percentage of subjects using rescue medication at different visits, the total dosage used and the duration of rescue medication use were summarised overall and by previous WHO-step analgesic group.
- The EQ-5D item scores and total scores and the EQ-5D health VAS scores will be summarised and graphed for Visit 1, Visit 4 and Visit 5, overall and by previous used analgesic. Absolute changes from baseline were summarised, ANCOVA analyses were performed on the changes from baseline in EQ-5D total scores and the EQ-5D VAS health scores at Visit 4. To compare the five EQ-5D item scores at Visit 4 with Visit 1 to see if changes in the EQ-5D item scores were statistically significant, the Bowker's test of symmetry was used, testing the null hypothesis of no change between Visit 1 and Visit 4.

Interim Analyses: Not applicable.

Post hoc Analysis: Initial analyses had incomplete data on daily dose of OXN, rescue medication use, laxative use and AE/related AE (ADR) overview. Due to SAS table limitations a post hoc analysis was performed completing the data. Post hoc analyses were performed for the daily dose of OXN (by WHO-Step Group and Constipation Group), subject preference of OXN compared to previous analgesic therapy at last visit (by WHO-Step Group and Constipation Group), with respect to Quality of Life and overall treatment compared to previous analgesic therapy at last visit, the use of rescue medication and daily dose of rescue medication (by WHO-Step Group and Constipation Group), daily dose of laxative use (by WHO-Step Group and Constipation group)and AE/related AE (ADR) overview (by WHO-Step Group and by Constipation Group).

Safety Analyses: The number of subjects with at least one adverse event (AE), with at least one serious adverse event (SAE), with at least one severe adverse event, with at least one study medication related adverse event, and with at least one adverse event causing stopping the study were summarised.

The number of adverse drug reactions reported, the maximal severity and maximal relation to OXN, the number of SAE's and the number of AE's continuing after study end were summarised. An AE was considered to continue after study end if no end date was reported or the end date was after the last visit date.

Sample Size Rationale: Sample size was considered for the response rate of patient preference of OXN with respect to quality of life at any time during treatment and with respect to pain relief. With 180 patients, an estimated overall response rate of 50% would have a precision of 7%, that is a two-sided 95% confidence interval would have a width of 14%. With 100 patients, the two-sided 95% confidence interval would have a width of 20%. With higher response rates the width of the 95% confidence interval would decrease. A response rate of 70% with 180 patients would yield a width of the 95% confidence interval of 13%. Assuming an equal amount of patients in the previous used WHO I step group and WHO II step group, with 90 patients in both groups, and a response rate of 50% in the previous WHO II step group, a difference in response rate of 25% between the two groups could have been detected with a power of 92%, a difference of 20% with a power of 74%, using a two-sided type I error of 5%.

Results:

Efficacy: The primary objective of this study was to assess patient preference of OXN compared to previous WHO step 1 or 2 analgesics with respect to quality of life. 34.9% of the patients assess the quality of life as 'better' or 'much better' compared to previous therapy at Visit 2 increasing to 56.0% at Visit 4. This indicates that for the majority of the patients, treatment with OXN results in a better quality of life compared to the previous analgesic therapy. Response rate in the FA population was 59.2% (95% CI 51.7% to 66.8%), meaning that 59.2% of the subjects preferred the study treatment compared to previous WHO step 1 or 2 analgesics with respect to quality of life. In the FA population, the response rate in the WHO Step 2 group (64.2%) was higher than in the WHO step 1 group (50.0%), and the response rate in the constipated group (60.9%) was higher than in the non-constipated group (58.1%). However, these differences were not statistically significant. At the level of patient preference of OXN compared to previous WHO step 1 or 2 analgesic therapy with respect to overall treatment, the response rate in the FA population was 58.0% (95% CI 50.4% to 65.6%). The response rates on overall treatment followed the same pattern as on quality of life: they were higher in the constipated group than in the non-constipated group; in the FA population, response rate in the WHO Step 2 group was higher than in the WHO step 1 group, for the PP population this order was reversed. However, these differences were not statistically significant. The pain NAS score decreased clearly over time in all groups after treatment with OXN. Subjects in the WHO Step 2 group, with a high pain NAS score at baseline, show the largest decrease between Visit 1 and Visit 2 (12 points both for the FA and the PP population). For both WHO Step groups and for both constipation groups, changes from baseline at all visits were statistically significantly different from 0. Only for the 7 subjects in the other previous used analgesic medication group, changes from baseline were not statistically significantly different from 0. At last visit, the mean change from baseline in pain NAS score for the FA population was 16.3 points for the WHO Step 2 group and 8.2 points for the WHO Step 1 group ($p = 0.034$). For the PP population, the mean change from baseline in pain NAS score at last visit was 17.8 points for the WHO Step 2 group and 11.8 points for the WHO Step 1 group ($p = 0.201$). Mean differences in decrease in pain NAS scores at last visit were not statistically significantly different between both constipation groups, while the mean differences in the constipated group were higher compared to the non-constipated group both for the FA population as for the PP population. Mean daily dose of OXN was 15.2/7.1 mg at start, increasing to 28.8/14.4 mg at last visit in the total group. No significant differences in mean daily dose were found between the subgroups over time. The number of patients with analgesic rescue medication use decreased over time and no differences were found for both WHP Step groups and both constipation groups. The mean daily dose of analgesic rescue medication decreased over time from 54.4 ± 61.7 mg at Visit 1 to 28.8 ± 56.9 mg at last visit. No differences in analgesic rescue medication use were found between subgroups and start and during treatment. OXN results in a significant decrease of pain over 4 weeks of treatment, while the addition of naloxone does not interfere with pain reduction. The effect of the treatment was measured with the BFI. However, this BFI did not show a significant changer over time in the total FA and PP population. Only for the constipated group, the median and mean changes from baseline in BFI at all visits were negative and showed a statistically significant improvement in BFI. The non-constipated group showed a statistically significant worsening in BFI. Changes from baseline in the number of bowel movements and the number of days with a bowel movement last 7 days were statistically significant different from 0 for the WHO Step 1 group at almost all visits, also at the last visit. The number of bowel movements and the number of days with a bowel movement decreased for these subjects during the study (a mean decrease of 1.5 bowel movements and 1.1 days with a bowel movement for the FA population at last visit and a mean decrease of 1.1 bowel movements and 0.9 days with a bowel movement for the PP population at last visit). For the subjects in the WHO Step 2 group, no significant changes were observed. Changes from baseline in both variables at last visit were statistically different between both WHO Step groups for the FA population and for the PP population. For the non-constipated group, the number of bowel movements and number of days with a bowel movement last 7 days decreased during the study, while these variables increased for the constipated group. For both groups, these changes from baseline were statistically significantly different from 0 at most visits. At last visit, these changes from baseline in the number of bowel movements and number of days with a bowel movement last 7 days were statistically significantly different between both

constipation groups. Concering the use of laxatives, more subjects changed from no laxative use at Visit 1 to yes laxative use at last visit (FA population: 21.4% in the WHO step 1 group and 17.9% in the WHO step 2 group) than the reverse (FA population: 1.8% in the WHO step 1 group and 6.6% in the WHO step 2 group). In the PP population, the same changes were observed. Comparison of laxative use at Visit 1 and at last visit, showed that for the non-constipated group the pattern of laxative use at both visits was statistically significant for the FA population and for the PP population, for the constipated group no statistically significant changes between laxative use pattern at both visits in laxative use was seen. Similar to the observations in the WHO step groups, more subjects in the non-constipated group changed from no laxative use at Visit 1 to yes laxative use at last visit (FA population 16.2%, PP population 15.7%) than the other way around at last visit (FA population 1.0%, PP population 1.4%).At the level of rescue medication, 65.1% of the subjects in the FA population used rescue medication at Visit 2, while this percentage was 55.6% at last visit (70.8% and 58.5%, respectively for the PP population). In both WHO step groups and in both constipation groups, the number of subjects using rescue medication decreased over time. The mean total EQ-5D score increased over time from 0.36 at Visit 1 to 0.55 at Visit 4 for the FA population (from 0.38 at Visit 1 to 0.57 at Visit 4 for the PP population), indicating an improvement in quality of life. No statistically significant differences are seen between both WHO step groups or between both constipation groups in changes from baseline in total EQ-5D score at Visit 4. Similarly, the EQ-5D VAS health scores increased over time from 49.9 at Visit 1 to 56.2 at Visit 4 for the FA population (from 49.2 at Visit 1 to 57.4 at Visit 4 for the PP population). Additionally, no statistically significant differences are seen between both WHO step groups or between both constipation groups in changes from baseline in EQ-5D VAS health score at Visit 4.

Safety: In total, 69.6% of the subjects from the safety population experienced an adverse event during the core study, which is comparable with previous randomized controlled trials. No deaths occurred during the core study. Most subjects showed mild adverse events (32.2%). The incidence of SAEs was low (1.2%) reported an SAE. In the total study group, 19.9% of the subjects stopped the study because of an AE. For 61.4% of the subjects, an adverse drug reaction was observed, 19.3% of the subjects stopped the study because of any adverse drug reaction and 28.7% of the subjects changed study medication because of an AE. Gastro-intestinal disorders (39.8%), with nausea (2.4%) and constipation (9.4%) as the most mentioned, and nervous system disorders (39.8%), with somnolence (21.6%) and dizziness (13.5%) as the most mentioned, were the most frequently reported disorders. The highest grade of relationship to study drug of reported adverse events was for 5.3% of the subjects indicated as definitely, for 56.1% of the subjects possibly or probably and for 8.2% of the subjects as not related or unlikely. In the extension phase, 61.8% of the subjects experienced an adverse drug reaction during the extension phase study. Two subjects (2.6%) reported an SAE. 9.2% of the subjects stopped the study because of an adverse drug reaction, while 14.5% of the subjects stopped study medication temporarily or definitely

Conclusions: This study shows that patients who used WHO-step 1 and/or WHO-step 2 analgesics before, prefer treatment with OXN with respect to quality of life and overall treatment. This preference does not depend on previously used analgesic treatment with WHO-step 1 or WHO-step 2 and constipation at start of the study. Constipated subjects show a significant and clinically relevant reduction in constipation (BFI) over time, while the pattern of laxative use remains the same. Although BFI increases in non-constipated subjects, it remains well below the level at which constipation is considered to occur. This shows prevention of constipation occurring with OXN.

Date of the Report: 12-Nov-2014