2. SYNOPSIS

<table>
<tr><td>Name of Company:
Mundipharma Research GmbH & Co. KG</td><td>INDIVIDUAL STUDY TABLE</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Name of Finished Product:
Targin®, Targinact®, Targiniq®</td><td rowspan="2">Referring to Part … of the Dossier
Volume: Page:</td></tr>
<tr><td>Name of Active Ingredient:
Oxycodone/Naloxone</td></tr>
<tr><td colspan="3">Title of the Study: A randomised, double-blind, 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 cancer pain</td></tr>
<tr><td colspan="3">Sites: The study was carried out at a total of 64 initiated sites, Australia: 3, Czech Republic: 7, France: 9, Germany: 13, Hungary: 7, Israel: 6, Netherlands: 7; Poland: 7; UK: 5</td></tr>
<tr><td colspan="3">Publication (Reference): None</td></tr>
<tr><td>Study Dates:
02-Nov-2007 to 01-Mar-2010</td><td>Study Status:
Completed</td><td>Phase of Development:
Phase 2</td></tr>
<tr><td colspan="3">Objectives:
The objective of this study was to demonstrate that subjects with moderate to severe cancer pain taking oxycodone/naloxone prolonged release tablets (OXN PR) have improvement in symptoms of constipation as measured by the Bowel Function Index (BFI) and laxative use compared to subjects taking oxycodone prolonged release tablets (OxyPR) alone. Bowel Function Index (BFI) was the mean of the following items (assessed weekly at Visits 1, 2, 6, 7, 8 and 9):
• 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).
Each of the above questions referred to the last 7 days for the subject.

A further objective was to demonstrate the comparability of OXN PR and OxyPR for the management of chronic cancer pain as assessed by the Brief Pain Inventory – Short Form (BPI-SF) and rescue medication use recorded by subjects. Bowel function (as measured by BFI) and pain (as measured by BPI-SF) were co-primary endpoints.

Other objectives:
• To assess subject's assessment of opioid-induced constipation, constipation symptom severity, impact and bothersomeness based on the PAC-SYM and PAC-SYM(b) (Patient Assessment of Constipation).
• To assess symptoms of withdrawal based on the Modified Subjective Opiate Withdrawal Scale (SOWS).
• To assess safety parameters.
• To assess quality of life aspects based on the EuroQol EQ-5D and EORTC QLQ-C30 (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core).</td></tr>
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Methodology: This was a randomised, double-blind, active-controlled, double-dummy, parallel group study using OXN PR and OxyPR to treat moderate to severe, chronic cancer pain. The study had three phases: a screening phase, a 4-week double-blind phase, and a 24 week extension phase. Following screening subjects stopped their pre-study opioid and laxative medication and were randomised to receive either OXN PR or OxyPR in the double-blind phase for a period of 4 weeks, during which study medication could be titrated up to a maximum of 120 mg/day of oxycodone PR. Open label oxycodone immediate release capsules (OxyIR) were available to subjects as rescue medication throughout the Double-blind treatment Phase. OxyIR could be taken at a dose of approximately 1/6 of the oxycodone PR dose, and could be taken as required by subjects to treat breakthrough pain. A maximum of 6 doses of OxyIR could be taken in 24 hours. If a subject regularly required more than 2 uses of rescue medication per day, the investigator may have increased the subject's dose of double-blind medication by 10 mg/day of OXN PR/OxyPR in a double-blind, double-dummy manner. Subjects receiving 120 mg oxycodone PR per day and regularly requiring more than two rescue doses of OxyIR were to be withdrawn from the study.

Throughout the double-blind treatment subjects were given bisacodyl tablets to take as a laxative rescue medication if required, usually if no bowel movement occurred within 3 days. However investigators could instruct their subjects that if they exhibited discomfort during this period they could take oral bisacodyl earlier than after 3 days as required to treat constipation. The maximum allowed number of bisacodyl intakes was 5 dosages within 7 consecutive days.

Open Label Extension Phase: (Results will be reported in a separate CSR) Subjects who completed the double-blind phase or who discontinued due to constipation but still fulfilled all screening inclusion and exclusion criteria had the option to enter the 24 week extension phase in which they received open-label OXN PR for up to 24 weeks. Rescue medication (OxyIR) and laxative medication (bisacodyl) was supplied for the first 7 days of the extension phase. Following completion/discontinuation of the study the subject was followed up by telephone for 7 days to collect non-serious adverse events and for 30 days to collect serious adverse events.

Number of Subjects: Planned: 180 randomised subjects, **Enrolled:** 224 subjects; **Randomised**: 185 subjects, **Full analysis I:** 183 subjects, **Full-Analysis II:** 157, **Double-blind Safety:** 184 subjects, subjects, **Per Protocol:** 133 subjects, **Completed** :133 subjects.

Indication and Main Criteria for Inclusion: Subjects were at least 18 years-old with a diagnosis of cancer and documented history of moderate to severe, chronic cancer pain that required around-the-clock opioid therapy. They were also receiving WHO step II or Step III analgesic medication and had constipation induced, or worsened by their opioid medication, as shown by the subject's medical need of regular intake of laxatives to have at least 3 bowel evacuations per week, or having less than 3 bowel evacuations when not taking a laxative, respectively and by the subject's self-assessment that their constipation was induced or worsened by their current pre-study opioid medication. Subjects were excluded if they required a dose >80 mg/day oxycodone PR at the start of the Double-blind Phase.

Test Treatment, Dose, and Mode of Administration Double-blind Phase:

Subjects randomised to OXN PR treatment received blinded OXN PR and matched OxyPR placebo.

Oxycodone/naloxone prolonged release tablets (OXN PR) 5/2.5, 10/5, 20/10 and 40/20 mg PR taken orally. Dosing was fixed and symmetrical (20, 30, 40, 50, 60, 70, 80, 90, 100, 110 and 120 mg/day oxycodone prolonged release).

Reference Treatment, Dose, and Mode of Administration: Double-blind Phase:

Subjects randomised to OxyPR treatment received blinded OxyPR and matched OXN PR placebo.

Oxycodone prolonged release tablets (OxyPR) 5, 10, 20 and 40 mg PR taken orally. Dosing was fixed and symmetrical (20, 30, 40, 50, 60, 70, 80, 90, 100, 110 and 120 mg/day oxycodone prolonged release).

Duration of Treatment: Pre-randomisation Phase: 3 to 10 days.

Double-blind Phase: 4 weeks.

Extension Phase: Up to 24 weeks (Results will be reported separately).

Treatment Schedule: At entry into the double-blind phase subjects were changed from pre-study laxatives and opioid, to study laxatives and a dose of OxyPR or OXN PR that was based on their prior dose and whether they needed an increase to control pain. The double blind treatment phase was 4 weeks. Titration of study medication was allowed during this period. Oxycodone immediate release (OxyIR) was available as rescue medication. If subjects regularly required 2 or more uses of rescue medication per day the investigator may have increased the subject's dose of OXN PR/OxyPR up to a maximum of 120 mg oxycodone PR per day.

Criteria for Evaluation:

Main Efficacy assessments:

- Bowel Function Index (BFI) (primary endpoint)
- Brief Pain Inventory Short-Form (BPI-SF) (Co-primary endpoint)
- Amount of laxative medication use
- Amount of analgesic rescue medication

Other efficacy assessments:

- Patient Assessment of Constipation Symptoms (PAC-SYM)
- Patient Assessment of Constipation Symptoms including bothersomeness questions (PAC-SYM(b))
- EuroQol EQ-5D
- EORTC QLQ-C30
- Number of bowel movements the subject has had in the last 7 days before the study visit and number of days the subject had a bowel movement in the last 7 days before the study visit

Safety: Safety was assessed by documentation of adverse events, clinical laboratory results, vital signs, physical examinations, electrocardiograms (ECGs) and Modified Subjective Opiate Withdrawal Scale (SOWS) and recorded on the standard CRF pages and SAE data form. Tumour progression and related serious events as e.g. hospitalisation for surgery/diagnostic procedures, life threatening status, or death caused by the underlying malignant disease were not considered, and were not reported as, serious adverse events if they were undoubtedly unrelated to study medication.

Statistical Methods: After completion of 50 subjects, an interim analysis (according to Bauer and Köhne (1994)) was performed. The interim analysis would stop the study if either: 1. the maximum p value of the hypothesis test on BFI is below 0.0102 and that of the test on pain is below 0.0038, or 2. the p value for the BFI test was above 0.5. Otherwise, if neither (1) nor (2) applied, the study was continued with new sample size calculated on the basis of the interim BFI and Pain data. However, the study was not to be continued without a preliminary inspection of the AE data.

The primary study endpoint was the Bowel Function Index score. This was calculated as the mean value of the 3 single items included in the BFI: Ease of defecation (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). All 3 items were to be present to calculate the mean score.

Descriptive statistics were presented for the BFI score by treatment group and visit (results were presented for the FA2 and PP population) and for BFI score at Visit 9 (FA2 population). The BFI score was also plotted over time (FA2 population).

The primary analysis was based on a comparison of the BFI scores at Visit 9 between the treatment groups. The objective was to show that OXN PR is superior to OxyPR.

The co-primary endpoint was 'Average Pain' score from the Brief Pain Inventory Short-Form (BPI-SF).

Descriptive statistics were presented for the 'Average Pain' score by treatment group and visit. The results were presented for the per-protocol population and the FA2 population.The 'Average Pain' score was also plotted over time for the per-protocol population.

The primary analysis was based on a comparison of the 'Average Pain' score at Visit 9 between the treatment groups using LOCF. The objective was to show that OXN PR is non-inferior to OxyPR

More detail on this and the statistical methods for other variables is presented in the SAP (Appendix 16.1.9 and elsewhere in this CSR.

Enrolled: All subjects who provided informed consent. (Total 224)

Randomised Population: All subjects who were randomised to receive study medication. (OxyPR 92; OXN PR 93; Total 185)

Per-Protocol: Subjects who received at least one dose of study medication during the Double-blind Phase and who sufficiently complied with the study protocol (OxyPR 71; OXN PR 62; Total 133).

Full-Analysis I (FA1): Subjects who were randomised and received at least one dose of study medication during the Double-blind Phase and who had at least one post-dose double-blind efficacy assessment (OxyPR 92; OXN PR 91; Total 183).

Full Analysis II (FA2): Subjects from the Full-Analysis I population, but subjects with missing values of the BFI score or subjects who discontinued within the first 14 double-blind days other than lack of therapeutic effect or AE constipation was excluded for this analysis (OxyPR 80; OXN PR 77; Total 157).

Double-Blind Safety: Subjects who received any dose of study medication (OxyPR 92; OXN PR 92; Total 184).

Results: In total 224 subjects were screened for entry into the study, 39 subjects were screening failures and 185 subjects were randomised into the Double-blind Phase. In total 92 subjects received OxyPR and 93 received OXN PR. One subject randomised to OXN PR was not dosed because she discontinued the study by her own choice before receiving study medication. Overall, 51 subjects (27.7%) prematurely discontinued the study, with a similar proportion of subjects discontinuing from each treatment group (27.2% for the OxyPR group and 28.3% for the OXN PR group). The most common reason for discontinuation in both treatment groups was AEs, which was in line with the expected adverse event profile of strong opioids in this patient population. More subjects from the OXN PR group (21.7%) than the OxyPR group (13.0%) discontinued due to AEs. More subjects withdrew due to subject's choice or discontinued due to lack of therapeutic effect in the OxyPR group (9.8% and 3.4%, respectively) than the OXN PR group (4.3% and 1.1%, respectively). All together 133 (72.3 %) subjects completed the study.

Efficacy:

Bowel Function Index: Primary Analysis

The primary analysis (LOCF) which adjusted for the interim analysis, showed a statistically significant treatment difference (p=0.010). This was supported by the PP analysis (p=0.001).

In the analysis of the full data set the improvement in BFI (LOCF) was statistically significant (LSMean Difference (SE) -11.14 (3.9971), 95% CI -19.03, -3.24, p=0.006). This result was supported by the sensitivity analyses using the BOCF approach (LSMean Difference (SE) -10.85 (3.9372), 95% CI -18.628, -3.073, p = 0.007, FA2 Pop.,Table 14.2.1.12) the MMRM with treatment by visit interaction (At Visit 9 LSMean Difference (SE) -10.8 (4.04), 95% CI -18.8, -2.8), p = 0.008, FA2 Pop., Table 14.2.1.10) the MMRM analysis assuming a constant treatment effect (LSMean Difference (SE) -12.36 (3.3875), 95% CI -19.05,-5.67, p < 0.001, FA2 Pop.,Table 14.2.1.11) and the analysis on the PP population ((LOCF) LSMean Difference (SE) -14.78 (4.1708), 95% CI -23.03,-6.531, p <0.001,Table 14.2.1.9). Taking these analyses into account, OXN PR is not only statistically significantly superior in respect to BFI but has also demonstrated a change that is clinically relevant.

Brief Pain Inventory (BPI-SF): Co-Primary analysis

The results of the LOCF analysis (LSMean Difference (SE) -0.011 (0.2795); 90% CI, -0.474, 0.452; p<0.001) for the PP population and also for the FA1 population (Table 14.2.2.8, LSMean Difference (SE) -0.016 (0.2568); 90% CI, -0.409, 0.440 p<0.001) confirm the non-inferiority of OXN PR to OxyPR (non-inferiority bound 1.0) and identical analgesic efficacy of both opioid treatments in cancer pain therapy. This is supported by the BOCF results. This result was also supported by a sensitivity analysis of the data using a MMRM Analysis in which both groups were found to be non-inferior across all visits, including at Visit 9 LSMean Difference -0.1 (0.36, (90% CI -0.5, 0.3, p<0.001).

BFI: Secondary Analysis

Ease of defecation results (during the last 7 days according to patient assessment, FA2 population) showed that at baseline subjects in both groups had a similar mean score for this parameter (Mean (SD) 67.13 (23.54) with OxyPR and 66.51 (21.24) for OXN PR at Visit 1). Actually, at randomisation the score in the OXNPR group tended to be a little higher than in the OxyPR group (Mean (SD) 64.36 (23.92) with OxyPR and 68.73 (18.67) with OXN PR). However, although the score for this parameter did reduce slightly during the course of the study for the OxyPR group, by Visit 9 the OXN PR group was showing the lowest score (Mean (SD) 53.56 (28.74) with OxyPR and 42.00 (29.92) with OXN PR). This result shows that by the end of the study, subjects in the OXN PR group felt that defecation had become easier.

Feeling of incomplete bowel evacuation results (during the last 7 days according to patient assessment, FA2 population) show that, as with the ease of defecation parameter, at Visit 1 the scores were similar in both groups (Mean (SD) 57.24 (29.79) with OxyPR and 55.13 (24.95) with OXN PR). At randomisation (Visit 2) the scores were also similar between the groups (Mean (SD) 57.63 (30.96) with OxyPR and 57.08 (25.71) with OXN PR). By Visit 9 the scores had lowered in both groups but were lowest in the OXN PR group (Mean (SD) 45.62 (33.29) with OxyPR and 35.93 (30.65) with OXN PR), showing that by the end of the study subjects in the OXN PR group had experienced a greater reduction in the mean number of times they felt that they had had an incomplete bowel evacuation.

Personal judgment of patient regarding constipation results (during the last 7 days, FA2 population) show that, as with the previous two parameters, by Visit 9 there was a greater reduction in the score with the OXN PR group than there was with the OxyPR group. At Visit 1 the scores were similar in both groups (Mean (SD) 68.69 (23.35) with OxyPR and 67.26 (19.66) with OXN PR). At randomisation (Visit 2) the scores were also similar between groups (Mean (SD) 65.20 (24.53) with OxyPR and 66.10 (22.28) with OXN PR). By Visit 9 the scores had lowered in both groups but were lowest in the OXN PR group (Mean (SD) 50.54 (31.17) with OxyPR and 40.47 (29.16) with OXN PR). This result indicates that by the end of the study, subjects rated the judgement of the constipation parameter lower in the OXN PR group than they did in the OxyPR group.

Laxative Intake: Secondary Analysis

Laxative use was assessed to determined whether the results of the BFI were affected by laxative use during the study. Only oral bisacodyl was allowed as rescue medication for constipation. For the subjects included in FA2, the mean total (SD) laxative intake in the OXN PR treatment group was around 20% lower than in the OxyPR group (OXN PR: 26.10 (27.60) mg; OxyPR: 32.69 (31.26) mg) and the median difference was 12.5mg. This difference was not statistically significant ($p = 0.1685$) but there was a clear shift towards less laxative doses in favour of OXN PR which is supported by the difference in the medians (27.5 mg with OxyPR and 15.0 mg with OXN PR). The lower laxative use in the OXN PR group, as well as the significantly lower BFI scores, demonstrates that subjects in the OXN PR group had significantly improved bowel function compared to those in the OxyPR group. Similar results were seen for the double-blind safety population.

BPI-SF: Secondary Analysis

The analysis of the pain subscale score of the BPI-SF, calculated as 4 multiplied by the mean of the responses to the four subscales 'WORST', 'LEAST', 'AVERAGE' and 'RIGHT NOW, using the per protocol population, resulted in similar scale values in both treatment groups throughout the Double-Blind Phase. At randomisation (V2) the average pain subscale scores (SD) were comparable in both treatment groups (OxyPR 16.21 (7.42), OXN PR 15.76 (7.20), and remained comparable until the end of the Double-Blind Phase (V9) with mean scores (SD) of 14.03 (7.24) for OxyPR and 13.35 (6.07) for OXN PR. Similarly the pain impairment scores in each treatment group mirrored each other closely at each visit during the study and that scores in both groups had tended to reduce by Visit 9. This points to a similar analgesic effect with OxyPR and with OXN PR.

Individual ‘worst’, ‘least’, ‘average’ and ‘right now’ pain subscales were also analysed (PP population). At Visit 9 the ‘Worst’ pain scores (mean (SD)) were 5.32 (2.48) for OxyPR and 5.45 (2.55) for OXN PR; ‘Least’ pain scores (mean (SD)) were 2.28 (1.69) for OxyPR and 2.00 (1.37) for OXN PR; ‘Average’ pain scores (mean (SD)) were 3.52 (1.80) for OxyPR and 3.50 (1.88) for OXN PR and ‘Right Now’ Pain scores (mean (SD) were 2.75 (1.94) for OxyPR and 2.52 (1.68) for OXN PR.

Rescue Analgesia: Secondary Analysis

In general, in both treatment groups the need for analgesic rescue medication was low (less than one intake per day) over the Double-Blind Phase for the per protocol population, both regarding the frequency of rescue medication intake and the doses that were taken further supporting the high analgesic efficacy of the prolonged release opioid medications given throughout the Double-Blind Phase (OXN PR, OxyPR). Subjects receiving OxyPR during the Double-Blind Phase took analgesic rescue medication on average (SD) 0.74 (0.72) times per day, while subjects receiving OXN PR took rescue medication 0.84 (0.73) times per day. Comparable results could also be observed with respect to the average number of capsules taken per day. Subjects receiving OxyPR during the Double-Blind Phase took on average (SD) 0.97 (1.09) capsules OxyIR per day, while subjects receiving OXN PR took on average 1.30 (1.39) capsules per day. This minimal difference with respect to the analgesic rescue medication intake was not statistically significant (number of times per day: $p = 0.3982$, Average capsules per day: $p = 0.2168$). Therefore, based on the average pain score and the comparable and low analgesic rescue medication intake, it can be concluded that OXN PR is non-inferior to OxyPR with respect to the analgesic efficacy.

Other Efficacy Analyses: PAC-SYM, PAC-SYM (b) and Quality of Life aspects based on the EuroQol EQ-5D and EORTC QLQ-C30

The QoL parameters did reveal comparable results in both treatment groups over time, which is mainly attributable to the high analgesic efficacy of OXN PR as well as OxyPR. However a more detailed analysis of specific and relevant aspects of constipation (PAC-SYM, PAC-SYM(b), EORTC QLQ-C30 constipation subscore) indicate an improved outcome for OXN PR compared to the OxyPR treatment which could contribute to an improved quality of life for many cancer patients treated with OXN PR.

Safety: In general. the number subjects with AEs was comparable in both treatment arms and approximately 20% of the documented AEs were AEs due to progression of tumour disease or increase in cancer pain. An overall summary of AEs is presented below.

Overall Summary of Adverse Events: Double-Blind Safety Population

Category	Oxycodone (N= 92) n (%)	Oxycodone/ Naloxone (N= 92) n (%)	Total (N=184) n (%)
Number of AEs	243	270	513
Number of Subjects with AEs	71 (77.2)	79 (85.9)	150 (81.5)
Number of related AEs [(a)]	62	77	139
Number of Subjects with related AEs [(a)]	32 (34.8)	35 (38.0)	67 (36.4)
Number of severe AEs	31	36	67
Number of Subjects with severe AEs	20 (21.7)	26 (28.3)	46 (25.0)
Number of severe related AEs	5	8	13
Number of Subjects with severe related AEs	5 (5.4)	7 (7.6)	12 (6.5)
Number of SAEs	31	43	74
Number of Subjects with SAEs	22 (23.9)	25 (27.2)	47 (25.5)
Number of related SAEs [(a)]	4	8	12
Number of Subjects with related SAEs [(a)]	3 (3.3)	5 (5.4)	8 (4.3)

Cross-reference: Table 14.3.1.1 and Listing 16.17

AE: Adverse Event. N: Number of subjects in population, n: Number of subjects with available data, %: Percentage based on N.

AEs coded using MedDRA version 10.1

[(a)] as assessed by the investigator

In both treatment groups, the majority of AEs were mild or moderate in nature and not considered to be treatment-related by the Investigator. The number of subjects reporting AEs was marginally higher in the OXN PR group (79 subjects [85.9%]) compared with the OxyPR group (71 subjects [77.2%]). The most frequently reported AEs were gastrointestinal disorders (nausea, vomiting, constipation and abdominal pain - nausea was reported by notably more subjects in the OxyPR group than the OXN PR group (13.0% vs. 7.6%)), general disorders such as peripheral oedema, asthenia, pain and drug withdrawal syndrome, abnormal laboratory test results, cancer pain and progression, anorexia, anaemia and headache. Gastrointestinal disorders, headache, anorexia, peripheral oedema, asthenia and drug withdrawal syndrome are consistent with the expected safety profile of opioid analgesics, although these events could also be related to the underlying disease. Thirty-two subjects (34.8%) in the OxyPR group and 35 subjects (38.0%) in the OXN PR group had AEs that were considered to be treatment-related by the Investigator (i.e. unlikely, possibly, probably and definitely related). A total of 62 out of 243 AEs (25.5%) in the OxyPR group and 77 out of 270 AEs (28.5%) in the OXN PR group were considered to be treatment-related.

Drug withdrawal syndrome was reported by more subjects in the OXN PR group (7.6%) compared with the OxyPR group (2.2%). However, there was no statistically significant difference between the treatment groups in the incidence of any commonly reported AE, with 95% CIs for the odds ratio encompassing 1 for all AEs including nausea and drug withdrawal syndrome.

Twenty-two subjects (23.9%) in the OxyPR group and 25 subjects (27.2%) in the OXN PR group experienced one or more SAEs. Of the 31 SAEs in the OxyPR group and 43 SAEs in the OXN PR group, four and eight, respectively, were considered to be treatment-related. The treatment-related SAEs were Grand Mal convulsion (unlikely/possibly related), pain (probably related), AST increased and ALT increased (possibly related) in the OxyPR group, and abdominal pain (two subjects), malignant neoplasm progression, catheter site infection (unlikely related), vomiting, anorexia, nausea (possibly related) and intestinal obstruction (possibly/unlikely related) in the OXN PR group. Eighteen subjects (nine [9.8%] in each treatment group) died during the study; 16 deaths were related to cancer progression and two (one in each treatment group) were due to cardiac events. None were considered to be related to study medication by the Investigator.

There were no notable differences in the incidence of AEs for subjects aged > 65 years compared with subjects aged ≤ 65 years in either treatment group and there were no clinically notable changes in laboratory tests, vital signs, ECGs or the SOWS score. No apparent safety concerns of treatment with oxycodone or oxycodone/naloxone were identified.

Conclusions:

- This study provides evidence that OXN PR is superior to OxyPR with regards to bowel function, and particularly with regards to reducing constipation as demonstrated by the BFI, in patients suffering from cancer pain.
- The improvement in bowel function with OXN PR demonstrated by the BFI was statistically and clinically significant, and was achieved with 20% less laxative use.
- The study demonstrated that OXN PR is non-inferior to OxyPR with respect to analgesic efficacy, shown by the average pain subscore of the BPI-SF, as well as the low analgesic rescue medication intake.
- The general quality of life parameters revealed comparable results in both treatment groups over time, which is mainly attributable to the high analgesic efficacy of OXN PR as well as OxyPR. However, a more detailed analysis of specific and relevant aspects of constipation (PAC-SYM, EORTC QLQ-C30 constipation subscore) suggested an improvement in these quality of life aspects for OXN PR compared with OxyPR.
- The incidence of AEs was similar in both the OxyPR and OXN PR treatment groups. The most frequently reported adverse drug reactions were consistent with the known safety profile of the opioid analgesic class of drugs. Modified SOWS total scores 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 summary, OXN PR demonstrated a statistically significant and a clinically relevant improved bowel function compared with OxyPR, without sacrificing any of the analgesic efficacy of the oxycodone component. Consequently, a favourable benefit to risk ratio could be demonstrated for OXN PR in cancer patients similar to the results from the Phase 3 studies in non-malignant pain conditions (Vondrackova *et al* 2008; Simpson *et al* 2008; Löwenstein *et al* 2009; Sandner-Kiesling *et al* 2010).

Date of the Report: 11 May 2011