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:
Oxycodone/naloxone prolonged-release tablets (OXN5/2.5; OXN10/5; OXN20/10, OXN40/20)</td><td>Referring to Part … of the Dossier</td></tr>
<tr><td>Name of Active Ingredient:
Oxycodone/naloxone combination</td><td>Volume: Page:</td></tr>
<tr><td colspan="3">Title of the Study: An exploratory, randomised, double-blind, single-dummy, placebo controlled, parallel group study to demonstrate the analgesic efficacy of oxycodone/naloxone prolonged release tablets (OXN PR) in addition to pregabalin compared to pregabalin alone in opioid-naïve subjects treated with pregabalin suffering from moderate to severe pain due to diabetic polyneuropathy.
Local Protocol Amendment 1 (Germany, 4 May 2009 and Czech Republic, 17 April 2009) changed the title of the study to: An exploratory, randomised, double-blind, single-dummy, placebo controlled, parallel group study to demonstrate the analgesic efficacy of oxycodone/naloxone prolonged release tablets (OXN PR) in addition to pregabalin compared to pregabalin alone in opioid-naïve subjects treated with pregabalin suffering from <u>severe</u> pain due to diabetic polyneuropathy.</td></tr>
<tr><td colspan="3">Investigators: The study was conducted at a total of 29 study sites, in Czech Republic (eight sites), Germany (nine sites), Hungary (six sites) and Romania (five sites).</td></tr>
<tr><td colspan="3">Publication (Reference): None</td></tr>
<tr><td>Study Dates:
13 July 2009 to 26 March 2010</td><td>Study Status:
Completed</td><td>Phase of Development:
Phase 2</td></tr>
<tr><td colspan="3">Objectives:
<u>Objective of main interest:</u>
• To show superior analgesic efficacy of OXN PR in addition to a subject's current dose of pregabalin compared to pregabalin alone based on the "Short-Form McGill Pain Questionnaire" assessed at each visit (Melzack, 1987).
<u>Further objectives:</u>
• To assess the frequency of pain rescue medication intake.
• To assess the "average pain over the last 24 hrs" as assessed at each visit (Numeric Rating Scale (NRS) 0 – 10).
• To determine that the bowel function of subjects receiving OXN PR is comparable to the bowel function of subjects receiving pregabalin alone based on the Bowel Function Index (BFI) assessed at each study visit.
• To assess severity and interference of pain based on the modified Brief Pain Inventory, Short Form (BPI-SF) (Cleeland & Ryan, 1994).
• To assess the laxative medication (bisacodyl) intake.
• To assess the stool consistency during the 12 week treatment phase based on the Bristol Stool Form Scale (BSFS).
• To assess overall health based on the SF-36 v2.
To assess quality of life based on EuroQol EQ-5D (Brook, 1996).</td></tr>
<tr><td colspan="3">Methodology: A 12-week, exploratory, randomised, double-blind, placebo-controlled, single-dummy, parallel group pilot study.</td></tr>
<tr><td colspan="3">Number of Subjects: It was planned to randomise a total of 80 subjects in a 1:1 ratio to receive OXN PR or placebo (40 subjects per treatment group). A total of 98 subjects were actually enrolled and randomised (48 to OXN PR and 50 to placebo); in the OXN PR group 43 (89.6%) subjects completed the study and 5 subjects prematurely discontinued the study (3 due to AEs and one each due to administrative reasons and subject choice). In the placebo group 48 (96.0%) subjects completed the study and 2 subjects prematurely discontinued the study (one each due to administrative reasons and subject choice).</td></tr>
</table>

Indication and Criteria for Inclusion: Male or female subjects aged 18 years and over, with type 1 diabetes (insulin-dependent diabetes mellitus [IDDM]) or type 2 diabetes (non insulin-dependent diabetes mellitus [NIDDM]).

Subjects had to be experiencing moderate to severe (in Hungary and Romania) or severe (in Germany and Czech Republic) pain due to diabetic/idiopathic polyneuropathy.

In Hungary, Romania and Germany this had to be confirmed by a score of ≥ 5 for their average pain over the previous 24 hours and by a Michigan Neuropathy Screening Instrument (MNSI) assessment score of ≥ 2.5 at the Screening Visit that required additional opioid therapy (20 to 80 mg OXN PR per day) for a minimum of 12 weeks.

In the Czech Republic, subjects had to have experienced diabetic/idiopathic polyneuropathy for at least 3 months confirmed by a score of ≥ 7 for their average pain over the previous 24 hours (Average Pain Scale, NRS 0 – 10) and by a MNSI assessment score of ≥ 2.5 at the Screening Visit that required additional opioid therapy (20 to 80 mg OXN PR per day) for a minimum of 12 weeks.

All subjects had to have been established on a maximum tolerated dose of pregabalin (up to 600 mg/day) for at least 1 month.

Test Treatment, Dose, and Mode of Administration: Oxycodone/naloxone prolonged release (OXN PR) tablets 5/2.5 mg (batch number: PN3388), 10/5 mg (batch number: PN3351), 20/10 mg (batch number: PN3343) and 40/20 mg (batch number PN3282) administered orally twice daily at 12-hour intervals.

Reference Treatment, Dose, and Mode of Administration: Matching placebo tablets for OXN PR tablets 5/2.5 mg (batch number: PN3226), 10/5 mg (batch number: PN3228), 20/10 mg (batch number: PN3229) and 40/20 mg (batch number PN3230) administered orally twice daily at 12-hour intervals.

Concomitant Medication Including Rescue:

Rescue Analgesic Medication

Rescue analgesic medication was paracetamol (APAP) 500 mg tablets, 1000 mg administered orally every 4-6 hours as required (prn). At the discretion of the Investigator, the APAP dose could have been lowered to 500 mg if the Investigator or subject felt that the dose was higher than what may be required as a rescue medication. If the dose was lowered to 500 mg, the lowered dose was counted as a full single dose for that subject.

- Subjects entering the double-blind phase were able to take APAP as rescue analgesic medication up to a total daily dose of 4 g. An analgesic rescue medication dose was defined as 1000 mg APAP (two tablets).

  The following sentence was added by Local Protocol Amendment 1 (Czech Republic, 17 April 2009): The maximum duration of intake of 4 g APAP was 10 consecutive days.
- Subjects who required more than 80 mg per day of oxycodone PR for adequate analgesia during the double-blind phase were to be discontinued from the study.
- During the double-blind treatment phase, subjects who consistently required more than 2 rescue doses of APAP per day were to have their dose of OXN PR increased. Up-titration could continue until the maximum dose of OXN 80/40 mg PR (OXN 40/20 mg PR twice daily) or respective placebo was reached. *'Consistently' was defined as >3 days per week in Local Protocol Amendment 1 (Germany, 4 May 2009).*
- During the double-blind phase, subjects who were on the maximum dose of study medication (80 mg oxycodone PR) and who consistently required more than 2 rescue doses per day were to be discontinued from the study. *'Consistently' was defined as >3 days per week in Local Protocol Amendment 1 (Germany, 4 May 2009).*
- Four rescue doses of APAP was the total maximum amount of rescue medication per day. Subjects who, on more than 2 consecutive days took more than 4 rescue doses were to be discontinued.
- APAP was the only allowed rescue pain medication during the double-blind phase. It was to be dosed no sooner than every 4 hours as needed.

The Investigator assessed the subject's use of rescue medication and made any necessary changes in study medication doses during telephone contacts and subject visits to the clinic.

Laxatives (Rescue Medication for Constipation)

Rescue medication for constipation was bisacodyl 5 mg tablets, 10 mg administered orally every 3 days prn. At the discretion of the Investigator, the bisacodyl dose could have been lowered to 5 mg if the Investigator or subject felt that the dose was higher than what may be required to provide an adequate bowel movement. If the dose was lowered to 5 mg, the lowered dose was counted as a full single dose for that subject.

During the double-blind phase, subjects were only permitted to take oral bisacodyl 10 mg per day as rescue medication for constipation. Bisacodyl tablets were to be used no sooner than 72 hours after the subjects' most recent Bowel Movement (BM). However, Investigators instructed the subject that if they had discomfort during the 72 hour period, they could take oral bisacodyl earlier than 72 hours after their most recent BM as required to treat constipation. If there was no BM within 24 hours following the 72 hour period after the most recent BM, bisacodyl use could have been repeated. If there was still no BM within 24 hours following the repeated use of bisacodyl, an enema could have been used. If there was still no BM following the use of the enema, the subject was to be discontinued from the study.

Duration of Treatment:

Pre-randomisation phase

Screening Phase - Prospective Assessment: Up to 14 days

Double-blind phase

Treatment with double-blind medication for 12 weeks (approximately 84 days).

Follow-up Phase: Subjects converted to marketed opioids, if required at the discretion of the Investigator and subject (7 days).

Total Duration: Up to approximately 105 days.

Treatment Schedule:

Pre-treatment phase:

Screening: At Visit 1, after written informed consent was obtained, subjects underwent complete evaluation for study eligibility (i.e., all inclusion/exclusion criteria). Subjects who met the prospective assessment criteria continued in the study.

Double-blind phase:

Following randomisation subjects attended 3 telephone Visits (V3, V4 and V5, if Visit 6 was earlier than Day 7 after randomisation then not all Visits 3-5 were completed) and 5 clinic Visits (V6, V7, V8, V9 and V10) and one follow-up visit (V11) which could be conducted as a telephone or clinic visit during the double-blind phase. At Visit 2, subjects received their study medication which was either OXN PR or OXN PR - matched placebo. The starting dose was OXN 10/5 mg PR twice daily, which could be titrated to an effective analgesic maximum daily dose of OXN 80/40 mg PR (OXN 40/20 mg PR twice daily).

APAP was available as rescue medication. Double-blind study medication was titrated according to the Investigator's assessment of the subject's analgesia during telephone contacts and visits by the subject to the clinic. During the double-blind phase subjects were only able to take oral bisacodyl as a laxative if it was required to treat constipation. At Visit 2 a commercial pack of bisacodyl was given to the subject. Subjects were not allowed to take self prescribed laxatives.

Criteria for Evaluation:

Efficacy Assessments:

- The Short-Form McGill Pain Questionnaire
- Analgesic rescue medication use
- Average Pain over last 24 hours (based on the Pain Intensity Scale).
- Bowel Function Index (BFI)
- Pain severity subscale score and interference of pain subscale score (from the modified BPI-SF Laxative use (frequency and amount)
- Stool consistency (using the BSFS)
- The SF-36 v2 health survey
- Health outcome as measured by EuroQol EQ-5D

Safety: Safety was assessed by documentation of adverse events, clinical laboratory test results, vital signs, physical examinations, and electrocardiograms (ECGs)

Statistical Methods:

Analysis of Main Interest

Superior pain control (as measured by the Short-Form McGill Pain Score) of the 'OXN PR' group to the 'placebo' group was tested by means of a one-sided (at a 0.025% significance level) unpaired two-sample t-test per visit. The sequentially rejective hypotheses testing procedure started at Visit 10 and then went back to any earlier visits (Visit 9 to Visit 6) when all previously tested visits provided statistically significant outcomes, respectively. Last Observation Carried Forward (LOCF) replaced any drop-outs after randomisation.

Further Efficacy Analysis

A mixed-model repeated measures (MMRM) analysis of covariance (ANCOVA) of the Analgesic Rescue Medication Intake was carried out for Visits 3 to 10 as the repeated measures. From this two-sided 95% confidence intervals for the difference of the treatment groups were derived. Also, a MMRM ANCOVA with two-sided 95% confidence intervals for the treatment difference of the Average Pain Over Last 24 Hours was carried out for Visits 3 to 10. MMRM ANCOVA was carried out on the modified BPI-SF for Visits 6 to 10 and Visit 2 as a baseline covariate. Two-sided 95% confidence intervals for the difference of the treatment groups were derived. Furthermore, frequency and amount of laxative use at Visits 6 to 10 were also analysed by means of a MMRM ANCOVA with 95% confidence intervals for the difference of the treatment groups. The change of Visit 10 to baseline in the EuroQol EQ-5D was analysed by means of 95% t-type confidence intervals. The change of Visit 10 to baseline in the SF-36 v2 health survey was analysed by means of 95% t-type confidence intervals.
The change of Visit 10 to baseline and that of Visit 8 to baseline in the BSFS was analysed by means of 95% t-type confidence intervals.

The t-test analyses used LOCF imputation with any missing data beyond Visit 2; the MMRM analyses did not use any missing data replacement or imputation approach.

All efficacy analyses were run on the Full Analysis Population. The safety analyses was performed on the Double-Blind Safety population.

Analysis Populations:

Enrolled: All subjects who provided informed consent.

Full-Analysis: Subjects, who were enrolled and received at least one dose of study medication during the double blind phase and who had one efficacy assessment based on the Short-Form McGill Pain Questionnaire.

Per-Protocol: Subjects who received at least one dose of study medication during the double-blind phase and who sufficiently comply with the study protocol (this population was defined prior to the unblinding of treatment assignments).

Double-blind Safety: Subjects who received at least one dose of study medication, and had at least one safety assessment after that dose.

Sample Size Rationale: Due to a limited amount of information being available it was assumed that pregabalin and gabapentin could be regarded as similar effective drugs in neuropathic pain treatment. The sample size was calculated for a significance level of 5% (one-sided) with 66% power. A within-treatment standard deviation (as with gabapentin) of 6.66 and a treatment difference of 3.1 (in the Short-Form McGill score) was assumed (as observed with a previous study, OXY3204) necessitating a sample size of 40 subjects per treatment group, or 80 randomised subjects in total (with a one-sided t-test).

Results: In the OXN PR group the mean age of subjects was 58 years (range 38-77 years); 13 subjects (27%) were aged greater than 65 years. Twenty five of the subjects (52%) in this group were female and 23 (48%) were male. In the placebo group the mean age of subjects was 62 years (range 45-80 years); 18 subjects (36%) were aged greater than 65 years. Twenty three subjects (46%) in this group were female and 27 (54%) were male. All subjects in the study were Caucasian.

Efficacy: McGill Pain Score

The McGill Pain Score is the sum of the answers to three questions: A – describe your pain during the last week, B – rate your pain during the last week, C: present pain intensity. The McGill Pain Scores at Visit 2 (randomisation) and Visit 10 (end of study) are presented below.

Summary of McGill Pain Scores: Full Analysis Population

McGill Score	Statistic	OXN PR (N=47)	Placebo (N=50)	Total (N=97)
McGill Sum Score Visit 2	n	47	50	97
	Mean (SD)	95.58 (16.42)	94.75 (20.00)	95.15 (18.26)
	Median	95.0	96.0	96.0
	Min, Max	64, 132	35, 130	35, 132
McGill Sum Score Visit 10	n	46	50	96
	Mean (SD)	47.65 (30.27)	49.56 (29.62)	48.64 (29.79)
	Median	40.0	48.5	45.5
	Min, Max	4, 117	0, 116	0, 117
	CI 95%			-14.088, 9.9029
	p Value			0.7298

At randomisation (Visit 2) the pain scores were similar between the groups. By the end of the double-blind phase (Visit 10) the scores had improved in both groups but the difference between the groups was not shown statistically significant.

Analgesic Rescue Medication Intake

During most of the double-blind phase the dose and frequency of intakes of analgesic rescue medication was similar between groups. However, at Visit 10 there was a slightly higher mean intake frequency in the placebo group (mean (SD) 3.98 (8.65) intakes with OXN PR vs 6.88 (12.73) intakes with placebo).

Average Pain over last 24 hours (based on Pain Intensity Scale)

The average pain score decreased in both groups during the study (from mean (SD) 6.94 (1.11) for OXN PR and 6.66 (1.65) for placebo at Visit 2 to mean (SD) 3.54 (2.11) for OXN PR and 3.72 (2.05) for placebo at Visit 10). However, a statistically significant difference between both groups has not been shown.

Bowel Function

The subjects' BFI scores in both groups were low at randomisation (BFI by visit with LOCF was mean (SD) 5.89 (12.92) for OXN PR and 9.18 (20.11) for placebo at Visit 2) and did not show a clinically significant change by the end of study (mean (SD) 10.44 (18.39) for OXN PR and 7.08 (12.98) for placebo at Visit 10) (a clinically significant change is defined as a change in BFI score of ≥ 12). Similar results were seen for BFI by visit for observed values.

The subjects in this study were opioid-naïve and the use of opioids commonly leads to opioid-induced constipation, therefore the lack of change in bowel function in the OXN PR group supports the assumption that OXN PR counteracts opioid-induced constipation.

Pain Severity and Interference of Pain (BPI-SF)

Subjects' pain severity subscore decreased from randomisation to end of study in both groups. The difference between the groups has not been shown to be statistically significant (BPI pain severity subscore by visit was mean (SD) 24.62 (5.13) for OXN PR and 24.76 (6.96) for placebo at Visit 2 and 12.85 (8.37) for OXN PR and 13.61 (7.62) for placebo at Visit 10).

Subjects' pain interference subscore decreased from randomisation to end of study in both groups. Again the difference between the groups has not been shown to be statistically significant (BPI pain interference subscore by visit was mean (SD) 37.98 (13.88) for OXN PR and 38.96 (14.99) for placebo at Visit 2 and 19.26 (15.62) for OXN PR and 22.24 (15.76) for placebo at Visit 10).

Laxative Use

Laxative use was very low throughout this study. At Visit 3, the first visit following initiation of study medication, the mean (SD) intake (times per day) was 0.00 (0.00) in the OXN PR group and 0.06 (0.31) in the placebo group. By Visit 10 the intake was still only 0.48 (2.03) in the OXN PR group and 0.66 (2.19) in the placebo group. The comparably low laxative intake in both groups, even after 12 weeks of treatment, is supportive of the assumption that OXN PR counteracts opioid-induced constipation.

Stool Consistency

During the study, subjects' stool consistency overall was similar in both groups and no trend towards a change in stool consistency was observed. From randomisation to Visit 10, in the OXN PR group 9 subjects' stools became softer (BSFS score increased), 20 subjects' stool consistency remained the same and 17 subjects' stool consistency became harder (BSFS score decreased). The corresponding numbers in the placebo group were, 14 subjects' stools became softer, 24 subjects' stools remained the same consistency and 12 subjects' stool consistency became harder.

SF-36 Health Survey

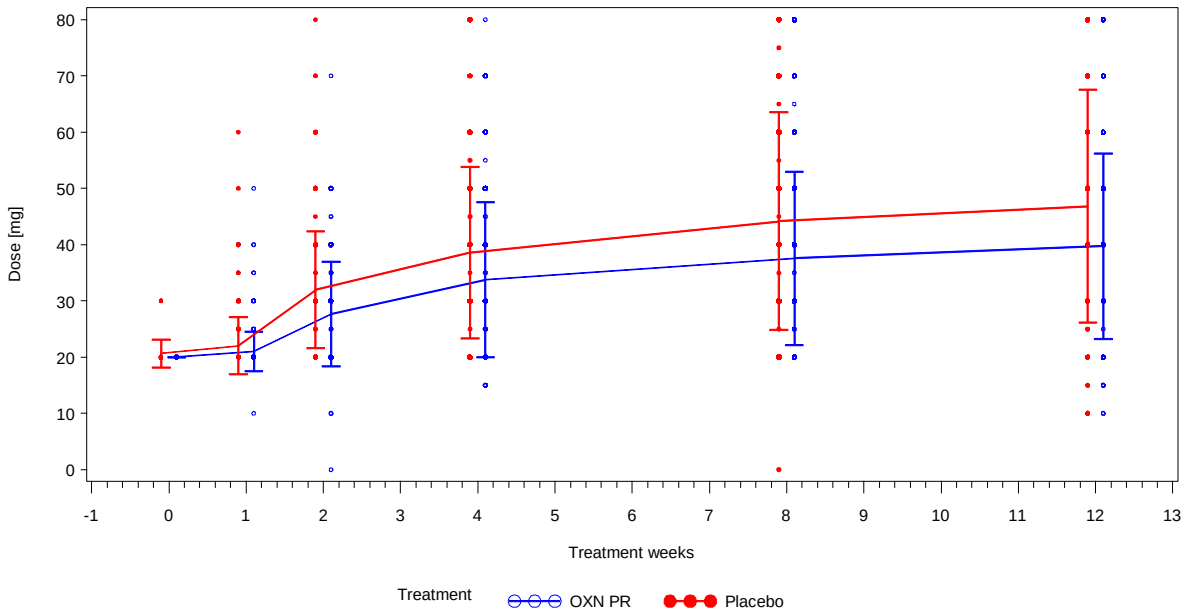
For the SF-36 Health Survey subscores (bodily pain, general health, mental health, physical functioning, role-physical, social functioning and vitality), the greater the score the better the health of the subject, and for all of these there was an increase from randomisation to Visit 10. The increases were of similar magnitude in both groups and there was no difference between the groups.

EuroQol EQ-5D Health Outcome

The EuroQol EQ-5D total score increased (improved) by the end of study in both groups (mean (SD) 0.35 (0.34) for OXN PR and 0.46 (0.30) for placebo at Visit 2; 0.65 (0.23) for OXN PR and 0.65 (0.20) for placebo at Visit 10). The score at randomisation was higher in the placebo group therefore the change in score was slightly greater for the OXN PR group.

Extent of Exposure

Figure 15.4
OXN2502: Extent of Exposure
Double-blind Phase
Full Analysis Population



Dose at Start = Dose of second Day of Study
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Study medication dose was continuously increased after the first treatment week. On average, up-titration was performed at each visit, and the placebo group began deviating from the OXN PR group the longer the treatment lasted. Typically, the need for up-titration should indicate uncontrolled pain which contrasts with the findings for average pain score and the McGill pain score.

Safety

Thirty six subjects in the OXN PR group (75%) and 22 subjects in the placebo group (44%) experienced AEs. 31 subjects (65%) in the OXN PR group and 14 subjects (28%) in the placebo group had AEs that were considered by the investigator to be treatment related. Of these subjects with related AEs, 21 in the OXN PR group and 11 in the placebo group, were ≤ 65 years old. The most common AEs were gastrointestinal (17 subjects (35%) with OXN PR; 10 subjects (20%) with placebo), nervous system (12 subjects (25%) with OXN PR; 5 subjects (10%) with placebo) and infections and infestations (9 subjects (18.8%) with OXN PR and 3 subjects (6%) with placebo). Four subjects experienced 5 SAEs whilst in the OXN PR group; one had coronary artery disease and iliac artery stenosis, one had cystitis, one had an abscess (all unrelated to study medication) and one had atrial fibrillation (unlikely to be related to study medication). There were no clinically significant trends for changes in laboratory data, or vital signs from the beginning to the end of the study and the only ECG abnormality that occurred at the last study visit but was not present at baseline (atrial fibrillation, as mentioned above) was unlikely to be related to study medication.

Conclusions: This trial was designed as an exploratory pilot study to obtain insight into the use of OXN PR with neuropathic pain, supplementing the findings of a previous study that compared OxyPR with gabapentin[1]. The analgesic potency of OxyPR with neuropathic pain has already been demonstrated[1] and potency is not affected by the addition of Naloxone[2, 3, 4, 5] . On the other hand, the safety profile of OXN PR with neuropathic pain could be slightly different and additionally gastrointestinal effects on opioid naïve subjects have been of interest.

Although we expected an elevated placebo effect with a study in neuropathic pain (and therefore retentively power the study) the actual size and duration of the effect was beyond what was expected. For instance, average pain in the placebo group decreased from 6.66 at Visit 2 to 3.72 at Visit 10, a reduction of 56%. This is far beyond what was expected for OXN PR and was well within a clinically relevant magnitude. However, the presence and size of the placebo-driven change did not allow any drug-related change to be assessed as long as it persisted, therefore, all respective analyses ended inconclusively.

To carry out a proper estimation and assessment of the drug effect, the maintenance phase would have had to be longer than the duration of the placebo effect and this did not occur in this study. Increasing drug doses with an incremental gap between the treatment group and the placebo group could be seen as a first sign of a declining placebo effect, but in fact up-titration might have continuously renewed subjects' belief that they were receiving an effective medication, thereby renewing the placebo effect.

The incidence of constipation in the OXN PR group is well below the expected incidence with normal opioid treatment, supporting the assumed opioid induced constipation-preventive ability of OXN PR. This is also underpinned by the results of the BFI questionnaire. The gastrointestinal safety data also seems to be affected by investigators' expectations, with 4 out of 5 constipation AEs assessed as related to study medication in the placebo group. This needs to be taken into account when considering the incidence of related constipation AEs in both groups. Overall, the number of constipation AEs for the OXN PR group was below what would be expected upon treatment with an opioid (without the naloxone component) so, for this study, this is a hint of the preventive efficacy of OXN PR with regards to opioid-induced constipation. Although this study alone cannot prove this, due to insufficient sample size and the unexpectedly strong initial placebo effect.

Therefore, all efficacy assessments failed to provide evidence for superior analgesic efficacy when OXN PR was added to pregabalin therapy and this study was inconclusive. The data in this study do not allow for a decision to be made upon the existence or non-existence of relevant efficacy outcomes, although previous confirmatory studies have proved relevant efficacy.[1,2, 3, 4, 5.] To compensate for the large placebo effect seen here an observational period would be required that would exceed the time at which the last up-titration was permitted, and also an essentially increased sample size would be required. This could be seen as ethically problematical for the limited information that would possibly be gained in addition to that already gained from the OxyPR/gabapentin study[1]; this exploratory pilot study has not uncovered fundamental new aspects of OXN PR treatment that need to be investigated further.

[1]. Hanna M et al., Prolonged-release oxycodone enhances the effects of existing gabapentin therapy in painful diabetic neuropathy patients. Eur J Pain. 2008 Aug;12(6):804-13.

[2.] Löwenstein O et al., Efficacy and safety of combined prolonged-release oxycodone and naloxone in the management of moderate/severe chronic non-malignant pain: results of a prospectively designed pooled analysis of two randomized double-blind clinical trials. BMC Clin Pharmacol 2010, 10:12.

[3]. Simpson K et al., Fixed-ratio combination oxycodone/naloxone compared with oxycodone alone for the relief of opioid-induced constipation in moderate to-severe noncancer pain. Curr. Med. Res. Opin. 2008, 24(12), 3503-3512.

[4]. Löwenstein O et al., Combined prolonged-release oxycodone and naloxone improves bowel function in patients receiving opioids for moderate-to-severe non-malignant chronic pain: a randomised controlled trial. Expert Opin Pharmacother 2009, 10(4), 531-543.

[5]. Vondrackowa D et al., Analgesic efficacy and safety of oxycodone in combination with naloxone as prolonged release tablets in patients with moderate to severe chronic pain. J. Pain 2008, 9(12), 1144-1154.

Date of the Report: 09 February 2012