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:</td><td>Referring to Part … of the Dossier</td></tr>
<tr><td>Name of Active Ingredient:</td><td>Volume: Page:</td></tr>
<tr><td colspan="3">Title of the Study: An exploratory, randomised, active-controlled, double-blind, double-dummy, parallel group pilot study to determine the ability of oxycodone/naloxone prolonged release tablets (OXN PR) to reduce the number of subjects developing symptoms of opioid induced constipation compared to morphine prolonged release tablets (MOR PR) in opioid naïve, non-constipated subjects with non malignant pain that require opioid treatment.</td></tr>
<tr><td colspan="3">Investigator(s): 35 centres: Czech Republic (15) Hungary (5) and United Kingdom (15).</td></tr>
<tr><td colspan="3">Publication (Reference): None</td></tr>
<tr><td>Study Dates:
25 Apr 08 to 1 Jan 09</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 demonstrate that in a group of opioid naïve non-constipated subjects with non malignant pain, treatment with OXN PR tablets leads to a higher responder rate compared to MOR PR. A responder was defined as a subject who met the following criteria:
• A subject, whose bowel function improved, did not change or did not have an unacceptable worsening compared to pre randomisation (subjective evaluation).

<u>Subjective evaluation:</u>
To what extent did your bowel function (e.g. frequency of defecation, stool consistency, ease of defecation, painful defecation) change during the treatment with study medication:

Bowel function is substantially improved
Bowel function is slightly improved
Bowel function is unchanged
Bowel function is slightly impaired, but still acceptable
Bowel function is substantially impaired, no longer acceptable

• A subject who did not discontinue from the study due to an AE of constipation during the first 14 ± 2 days of the double-blind phase.</td></tr>
<tr><td colspan="3"><u>Further Objectives:</u>
The following criteria were cross-checked for plausibility against the responder criterion
• Subject’s stool frequency during the study did not decrease by more than 50% compared to baseline (last 7 days before randomisation).
• A subject who did not take laxatives on more than 2 occasions during the four week treatment period.
• A subject in which the BFI score did not increase by an average of >11 during the double-blind phase compared to baseline (randomisation).</td></tr>
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Additional objectives were:

- Assessment of the Bowel Function Index (BFI)
- Assessment of Laxative intake
- Assessment of Stool frequency
- Incidence and kind of related adverse reactions
- To assess the BPI-SF at each study visit during treatment with study medication (OXN PR, MOR PR).
- To assess the frequency of pain rescue medication intake
- To assess the stool consistency during the 4 week treatment period
- To assess urinary function during the 4 week treatment period (subjective evaluation).

Methodology: This was a 4-week, exploratory, randomised, double-blind, active-controlled, double-dummy, parallel group pilot study to compare OXN PR and MOR PR in the number of subjects developing symptoms of opioid induced constipation following commencement of treatment with the opioid.

Opioid naïve, non constipated subjects suffering from non malignant pain who took no laxatives during the past 3 months were randomized to receive either OXN PR or MOR PR tablets. The maximum allowed dose of OXN PR was 20/10 mg taken every 12 hours and the maximum dose of MOR PR tablets was 40 mg taken every 12 hours. Subjects were allowed to take rescue analgesic medication for the treatment of breakthrough pain. Subjects randomised to OXN PR received oxycodone immediate release (OXY IR) as rescue medication and subjects randomised to MOR PR received Sevredol (MOR IR) tablets. Subjects were only to take a dose of rescue medication if their pain was uncontrolled.

If subjects experienced constipation throughout the double-blind treatment phase, subjects were given bisacodyl tablets to take as a laxative medication. Bisacodyl tablets could be used no sooner than 72 h after the subjects' most recent BM. However investigators could instruct their subjects that if they exhibited discomfort during the 72 hour period they could take oral bisacodyl as a laxative earlier than 72 hours after their most recent bowel movement as required to treat constipation.

Number of Subjects: Planned: 120 subjects, Screened 104 subjects. Planned to randomise: 80 subjects. Randomised: 96 subjects (48 in each group). Completed: 66 subjects (33 in each group).

Indication and Criteria for Inclusion: Male or female subjects of at least 18 years or older with a documented history of non malignant pain (e.g., Low Back Pain, Osteoarthritis, Neuropathic pain) that required opioid therapy (20-40 mg OXN PR per day or 40 - 80 MOR PR per day) for a minimum of 4 weeks. Subjects must not have reported constipation within the last 3 months, and subjects must not have taken laxative medication in the 3 months before the start of the study. Subjects must not have received opioid containing medication in the last 6 months on a regular basis (i.e. prescribed medication or more than occasional self medication use for cough/cold etc).

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

Test Medication	Dosage Form	Unit Strength	Dosing Frequency	Mode of Administration
OXN PR	Tablets	5/2,5, 10/5, 20/10 mg OXN PR	q12h	Oral
Matched placebo for MOR PR	Tablets	Matching placebo for 10, 30 mg MOR PR	q12h	Oral

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

Reference Medication	Dosage Form	Unit Strength	Dosing Frequency	Mode of Administration
MOR PR	Tablets	10, 30 mg MOR PR	q12h	Oral
Matched placebo for OXN PR	Tablets	Matching placebo for 5/2,5, 10/5, 20/10 mg OXN PR	q12h	Oral

Duration of Treatment: Pre-randomisation Phase: Screening Period - Prospective Assessment: Up to 7 days. Double-blind Phase Treatment with double blind medication for 4 weeks. Follow up Period: Subjects converted to marketed opioids (7 days). Total Duration: Up to approximately 42 days.

Treatment Schedule:

Screening: At Visit 1, after written informed consent is obtained, subjects underwent complete evaluation for study eligibility (i.e., all inclusion/exclusion criteria). Subjects meeting the Prospective Assessment Criteria could continue in the study.

Double blind Phase: Following randomisation subjects attended up to 3 telephone visits (V3, V4 and V5) in the week before Visit 6, and 3 clinic visits (V6, V7, V8) during the double-blind phase. At Visit 2, subjects received their opioid therapy which was either OXN PR or MOR PR tablets. The starting dose was OXN PR 10/5 mg bid, which could be titrated to an effective analgesic dose between 20/10 – 40/10 mg/day. Subjects randomised to MOR PR could start the treatment with MOR PR 20 mg bid which could be titrated to an effective analgesic dose between 40 mg and 80 mg/day. OXY IR or MOR IR 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 study site. During the double-blind phase subjects were able to take bisacodyl as a laxative if it was required to treat constipation. Subjects were not allowed to take self-prescribed laxatives.

Criteria for Evaluation:

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 subjective bowel function assessment data (at least Visit 7) or discontinued due to an AE of constipation.

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

Efficacy Assessment(s):

Efficacy variable of main interest - Responder rate based on:

- Subjective evaluation of bowel function
- AEs of constipation leading to discontinuation of the subject

Safety: Safety was assessed through documentation of adverse events, clinical laboratory results, vital signs, and electrocardiograms (ECGs) and recorded on the standard CRF pages and SAE data form.

Statistical Methods: Efficacy Analyses: The efficacy analysis on the variable of main interest was carried out using Fisher's exact test at a 5% significance level (one-sided) applied on the responder rates found with the MOR PR and OXN PR treatment. Further analyses on the cross-check plausibility variables were carried out by means of one-sided tests. Furthermore, any efficacy variables (of main interest and secondary) were listed by subject and summarised by means of descriptive statistics (e.g. number of non-missing data, arithmetic average with standard deviation, and median). All efficacy analysis used the full analysis population. Exploratory Post hoc Analyses: Lax-, BFI- and stool-adjusted Bowel Function Responder criteria were assessed by means of Fisher's exact test to visualise the cross-check variables' influence on the primary efficacy variable. Additionally, a one-sided Wilcoxon statistic was used to test the subjective Bowel Function response scores versus omnibus analysis, apart from any specific choice of a responder cut-off.

Results:

Efficacy:

Bowel Function Responder Assessments: Full Analysis Population

Parameter	Statistic	OXN PR (N=36)	MOR PR (N=35)	Exact (right) p value
Bowel Function Responder	N (%)	33 (91.67%)	29 (82.86%)	0.2248
Adjusted Bowel Function Responder	N (%)	12 (33.33%)	14 (40.00%)	0.7964
Lax-adjusted Bowel Function Responder	N (%)	26 (72.22%)	18 (51.43%)	0.0591
BFI-adjusted Bowel Function Responder	N (%)	16 (44.44%)	16 (45.71%)	0.6352
Stool-adjusted Bowel Function Responder	N (%)	27 (75.00%)	27 (77.14%)	0.6872

The number of bowel function responder subjects was 33 (91.67%) in the OXN PR group and 29 (82.86%) in the MOR PR group. The number of adjusted bowel function responder subjects was 12 (33.33%) in the OXN PR group and 14 (40.00%) in the MOR PR group.

All of these parameters are affected by the fact that they are based on subjective answers to a question, as well as by other confounding factors. Because of this, analysis of further plausibility variables was planned during the design of the study as a means of cross checking the bowel function responder assessment; the adjusted bowel function analysis (comprising of all 'cross check' plausibility variables) was one such analysis. Laxatives are commonly given to treat impaired bowel function so laxatives (bisacodyl only) were allowed in this study as an additional treatment, therefore another cross check, the laxative (lax)-adjusted bowel function responder analysis, was identified as important in this study because laxative intake temporarily influences the real effect of study medication on bowel function.

The lax-adjusted bowel function responder result corresponds to the number of subjects who were bowel function responders (bowel function substantially improved, slightly improved, unchanged or slightly impaired but still acceptable) but who also did not take laxatives more than twice during the study. Of these subjects, 26 (72.22%) were in the OXN PR group and 18 (51.43%) were in the MOR PR group.

Subjective Bowel Function Assessment: Full Analysis Population

Subjective Bowel Function Assessment	OXN PR N=36 n(%)	MOR PR N=35 n(%)
Bowel function is substantially improved	0 (0.0%)	1 (2.9%)
Bowel function is slightly improved	4 (11.1%)	2 (5.7%)
Bowel function is unchanged	14 (38.9%)	8 (22.9%)
Bowel function is slightly impaired, but still acceptable	15 (41.7%)	18 (51.4%)
Bowel function is substantially impaired, no longer acceptable	3 (8.3%)	6 (17.1%)
P-value (Wilcoxon Test, one-sided)	0.0580	

The table above goes beyond the simple bowel function responder 'yes or no' analysis and presents the number of individual responses to the subjective bowel function assessment question. From this the detail at other levels is visible and it can be seen that there is a trend towards more 'unchanged' or 'improved' bowel function assessment responses in the OXN PR group than the MOR PR group. The total number of subjects with a subjective bowel function assessment of substantially improved, slightly improved or unchanged was 18 (50%) in the OXN PR group and 11 (31.5%) in the MOR PR group.

Summary of 'Average Pain ' by Time Period: Full Analysis Population

Visit	Statistic	OXN PR (N=36)	MOR PR (N=35)
2	N	36	35
	Mean (SD)	6.17 (1.52)	5.71 (1.45)
	Median	6.0	5.0
	Min, Max	3, 9	3, 9
6	N	34	33
	Mean (SD)	4.88 (2.20)	4.24 (1.79)
	Median	5.0	5.0
	Min, Max	0, 9	0, 8
7	N	34	32
	Mean (SD)	4.62 (2.34)	4.13 (2.04)
	Median	4.0	4.0
	Min, Max	0, 9	0, 8
8	N	36	35
	Mean (SD)	4.39 (2.42)	3.34 (2.13)
	Median	4.0	4.0
	Min, Max	0, 9	0, 8

Although the dose of MOR PR was double that of OXN PR, the average pain results did not show a statistical difference (p=0.183). The 'average pain' table shown previously demonstrates that the doses of OXN PR and MOR PR used had more or less equal analgesic effect. Subjects in both groups had slightly higher levels of average pain at baseline (Visit 2) that levelled by Week 1 (Visit 6) and continued at a stable level until the end of the study. In addition there was a low level of supplemental analgesic use in both groups, confirming that pain was well controlled with study medication.

All further objectives are consistent with the findings reported above, including BFI, laxative use and stool frequency and consistency. There was no clinically relevant difference in BPI between the OXN PR and MOR PR groups. The frequency of pain rescue medication was equal between groups, although the mean dose of rescue medication was higher in the MOR PR group because higher doses of morphine were needed to produce an equi-analgesic effect to OXN PR. There were no statistically significant findings for urinary function.

Safety:

Common Adverse Events, Incidence (≥10%) in any Treatment Group, by System Organ Class (≥6%): Double Blind Safety Population

System Organ Class	OXN PR (N=47)	%	MOR PR (N=47)	%	Total (N=94)	%
Any AE	28	59.6%	35	74.5%	63	67.0%
Related AEs	26	54.2%	35	72.9%	61	63.5%
Gastrointestinal disorders	24	51.1%	34	72.3%	58	61.7%
Nervous system disorders	6	12.8%	10	21.3%	16	17.0%

Cross Reference: Table 14.4.2.9b and Appendix 16.2.4.4.2
Note: MedDRA System Organ Classes and Preferred Terms are listed alphabetically.

Overall, the number of subjects experiencing any AE is slightly higher in the MOR PR (n=35 (74.5%)) treatment arm compared with OXN PR (n=28 (59.6%)). Gastrointestinal disorders were the most frequently reported AEs in each group. These AEs are consistent with the expected AE profile of the opioid analgesic class of drugs represented by OXN PR and MOR PR. The majority of AEs were mild or moderate. No deaths were reported during the study. There was one SAE of retinal artery occlusion. This occurred in one subject (104601), 11 days before the start of the study and was not considered to be related to study medication. The subject was hospitalised for the condition on the first day that he received study medication, however he continued study medication uninterrupted and subsequently completed the study.

No clinically relevant findings were observed during the study for laboratory results, vital signs or ECGs.

Conclusions:

OXN2501 was designed to assess the prevention of constipation in subjects who were opioid-naive. In these study subjects bowel function was improved on average with OXN PR compared to MOR PR, particularly in terms of the subjective bowel function assessment, the laxative-adjusted bowel function responder assessment, the bowel function index and laxative intake.

With regards to pain assessment, both groups had similar analgesic efficacy but with OXN PR this was achieved at approximately half the dose, and with approximately half the dose of rescue medication, than with MOR PR. OXN PR also had a superior safety profile.

Sample data in this pilot study supports initial assumptions of the preventative effect of OXN PR compared with MOR PR in terms of bowel function in this study; however these assumptions cannot be transferred to the population in general because of a lack of statistical significance. A study to further investigate the preventative aspect of OXN PR would probably have limited evidence based on identified confounding factors and the lack of a validated endpoint focusing on opioid naïve patients and also taking into account the laxative intake.

Date of the Report: 07 Jan 10