3. SYNOPSIS

<table>
<tr><td>Name of Company:
Mundipharma Research GmbH & Co. KG
Höhenstrasse 10
65549 Limburg / Lahn
Germany</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 PR)</td><td rowspan="2">Referring to Part IV of the Dossier

Volume: Page:</td></tr>
<tr><td>Name of Active Ingredient:
Oxycodone/naloxone combination</td></tr>
<tr><td colspan="3">Title of the Study:
An open-label extension study (OXN3006S) following on from a randomised, double-blind, double-dummy, parallel-group multicenter study (OXN3006) to demonstrate improvement in symptoms of constipation in subjects with non-malignant pain taking oxycodone equivalent of 60 - 80 mg/day as oxycodone / naloxone prolonged release (OXN) compared to subjects taking oxycodone prolonged release tablets alone.</td></tr>
<tr><td colspan="3">Investigator(s)/Center(s) for Extension Phase:
Germany: 57 sites, Czech Republic: 13, Finland: 2, Hungary: 1; Germany: 32, Netherlands: 2; UK: 5, Spain: 2</td></tr>
<tr><td colspan="3">Publication (Reference): None</td></tr>
<tr><td>Study Dates:
04-Sep-2006 to 14-July-2008</td><td>Study Status:
Completed</td><td>Phase of Development:
Phase 3</td></tr>
<tr><td colspan="3">Objectives: To assess the long-term safety and efficacy of OXN PR in subjects with non-malignant pain, over a period of 12 additional months following on from the core study (OXN3006)</td></tr>
<tr><td colspan="3">Methodology: This was an uncontrolled, open-label study using OXN PR to treat moderate to severe, chronic non-malignant pain.</td></tr>
<tr><td colspan="3">Number of Subjects:
Planned: 266 randomised subjects. Completed Core study (Double-blind Phase): 222 subjects, Extension Phase: 216 subjects entered the Extension Phase, 216 subjects received study medication, 172 subjects completed the Extension Phase. In a subgroup of patients taking more than 80/40 mg OXN PR per day, 61 subjects entered and 52 completed the Extension Phase.</td></tr>
<tr><td colspan="3">Indication and Criteria for Inclusion:
Subjects must meet the following criteria to enter the Extension Phase:
1. Completed the Double-blind Phase.
2. Required continuation of daily opioid analgesic treatment, and were likely to benefit from chronic opioid therapy for the duration of the Extension Phase.
3. Willing and able to participate in all aspects of the Extension Phase, including use of open-label OXN PR, completion of subjective evaluations, attending scheduled clinic visits, and compliance with protocol requirements.</td></tr>
<tr><td colspan="3">Test Treatment, Dose, and Mode of Administration:
OXN10/5 mg PR, OXN20/10 mg PR, OXN40/20 mg PR, oral, q12h</td></tr>
<tr><td colspan="3">Reference Treatment, Dose, and Mode of Administration: None</td></tr>
<tr><td colspan="3">Duration of Treatment: up to 52 weeks</td></tr>
<tr><td colspan="3">Treatment Schedule: Subjects received open-label OXN PR (10/5 mg OXN PR, 20/10 mg OXN PR, 40/20 mg OXN PR) twice daily up to maximum daily dose of 120 mg OXN PR up to 52 weeks.</td></tr>
</table>

Criteria for Evaluation:

Efficacy:
There was no primary efficacy endpoint that the study was powered for, however, BFI, average pain (as measured by the pain intensity scale) frequency of rescue medication use (for the first week), and treatment satisfaction (TSQM) scores were measured

Safety: Safety was assessed using adverse events, clinical laboratory results, vital signs, physical examinations, SOWS; and electrocardiograms (ECGs).

Statistical Methods: Analysis of efficacy and safety data across the Extension Phase was performed separately from the analysis of the Double-blind Phase.

Total Exposure Safety: The total exposure safety population consists of the subjects who receive at least one dose of OXN in the Double blind or Extension Phase and have at least one safety assessment after the first of such doses.

Subgroup Population: The subgroup population consists of those subjects of the total exposure population who received a total daily dose of more than 80/40 mg OXN PR per day on more than 7 consecutive days.

Results:

Efficacy: BFI

Subjects on OXN PR continued the trend seen in the OXN3006 core study, in that the BFI score reduced throughout the Extension Phase. By the end of the Extension Phase the mean (SD) BFI had reduced from 38.7 (28.65) at Visit 9 to 23.3 (23.73) by Visit 15, which is a mean reduction of 15.4 points on the BFI score.

A post-hoc analysis of BFI scores split by the treatment that subjects received during the Double-blind Phase of the core study (OXN3006), shows that while all subjects continued to show a reduction in BFI values during the Extension Phase, this reduction was greatest in those subjects who switched from Oxycodone PR to OXN PR at the beginning of the Extension Phase.

In the subgroup of subjects receiving a total daily dose of more than 80/40 mg OXN PR per day on more than 7 consecutive days the mean (SD) BFI reduced from 39.1 (28.99) at Visit 9 to 24.1 (24.81) by Visit 15, which is a clinically relevant mean reduction of 15 points on the BFI score.

Average Pain

Subjects had reached stable pain control during the Run-In phase of the core study (see OXN3006 CSR). Mean 'average pain' scores were very similar at each visit in the Extension Phase (between 3.7 and 4.1); these mean 'average pain' scores were also similar to those seen in the Oxycodone PR and the OXN PR group during the core study (At Visit 8 of the Double-blind Phase (Table 14.2.2.1a in OXN3006), mean (SD) Oxycodone PR was 3.94 (1.484); mean (SD) OXN PR was 4.13 (1.636); Total mean (SD) was 4.04 (1.561) vs mean (SD) OXN PR of 4.1 (1.83) at Visit 15 of the Extension Phase). These results confirm that stable pain control was maintained with OXN PR throughout the duration of the Extension Phase.

The mean pain intensity over the last 24 hours in the subgroup of subjects receiving a total daily dose of more than 80/40 mg OXN PR per day on more than 7 consecutive days was comparable to the end of the Double-Blind Phase (Total mean (SD), V8 = 4.40 (1.529) and remained stable over 6 months (Mean (SD), V13 = 4.5 (1.68)) and 12 months (Mean (SD), V15 = 4.2 (1.64)).

Analgesic Rescue Use

Analgesic rescue was only provided for the first week of the Extension Phase and after the first week was recorded as concomitant medication. The mean amount of analgesic rescue medication intake was low (0.6 (0.70) capsules per day) and similar to that seen at the end of the Double-blind Phase (0.85 (0.72) capsules per day). The mean daily use (as measured in mg) was only slightly higher during the first 7 days of the Extension Phase (mean (SD) = 6.81 (10.21 mg)) compared with the end of the Double-blind Phase (5.22(8.23 mg). The mean daily supplemental analgesic use also had no correlation with the dose of

oxycdodone/naloxone PR.

The mean frequency of analgesic rescue medication intake in the subgroup of subjects receiving a total daily dose of more than 80/40 mg OXN PR per day on more than 7 consecutive days (0.8 (0.74) capsules per day) was similar to that seen at the end of the Double-blind Phase (0.7 (0.75)). The mean daily supplemental analgesic use also had no correlation with the dose of oxycdodone/naloxone PR in the subgroup population. Treatment Satisfaction Questionnaire for Medication (TSQM) scores were quite high for all subjects, indicating that they were satisfied with the treatment that they were getting during the study.

Safety: The adverse events observed in this study were consistent with the expected adverse event profile of the opioid analgesic class of drugs. 159 subjects (73.6%) experienced adverse events, whereas only 93 subjects (43.1%) experienced adverse events that were related to study drug (i.e. definitely, probably, possibly or unlikely to be related). Regarding all reported AEs, the most common were musculoskeletal and connective tissue disorders (70 subjects (32.4%)) which were mostly due to the underlying disease. The next most common adverse events were gastrointestinal disorders (56 Subjects (25.9%)) and nervous system disorders (45 subjects (20.8%)) which are not unusual for a strong opioid. There were 19 subjects (8.8%) who experienced constipation, 7 (3.2%) of whom experienced constipation that was not related to study drug. 12 subjects (5.6%) experienced diarrhoea, whereas only 8 (3.7%) were reported as having diarrhoea related to study drug. 34 subjects experienced a total of 54 serious adverse events; of these 23 SAEs in 12 subjects were thought by the investigator to have a positive causal relationship to study medication. There was one death in this study. This was due to sepsis and was not considered by the investigator to be related to study medication.

In the subgroup of subjects receiving a total daily dose of more than 80/40 mg OXN PR per day on more than 7 consecutive days the incidence and kind of adverse events observed were consistent with the total exposure safety population. 48 subjects (78.7%) experienced adverse events whereas only 30 subjects (49.2 %) experienced adverse events that were related to study drug. Regarding all reported AEs, the most common adverse events experienced were musculoskeletal and connective tissue disorders (23 subjects (37.7%)), nervous system disorders (17 subjects (27.9%)), gastrointestinal disorders (15 Subjects (24.6%)) and general disorders and administration site conditions (15 Subjects (24.6%)). There were 5 subjects who experienced constipation (8.2%) and 4 subjects who experienced diarrhoea (6.6%).

Subjective Opiate Withdrawal Scales (SOWS) were stable during the Extension Phase (in the total population and the subgroup) and were similar to those seen during the Double-blind Phase, indicating that drug withdrawal was not a problem with OXN PR.

Mean values for haematology and blood chemistry parameters remained stable over the time course of the study. Isolated cases of abnormal values with respect to blood pressure or liver enzymes have already been covered by labeling in the respective product information.

There were no significant ECG findings. Based on the ECG data available in this study, no ECG abnormality was directly attributable to study medication.

Conclusions: Average pain scores remained stable throughout the extension study and analgesic rescue use was low, confirming that analgesic efficacy of OXN PR was maintained in the long term. Upon deeper analysis of the adverse events or suspected adverse drug reaction there are no safety concerns arising from the use of OXN PR tablets. Importantly, there were no new or unexpected adverse reactions observed which were attributable to the administration of OXN PR. Therefore, the safety profile of OXN PR in the investigated doses is consistent with those of other strong opioids. This study provides evidence that OXN PR is safe and efficacious for long-term therapy in subjects with non-malignant pain and also demonstrated that the improvement in bowel function seen with OXN PR during the core study (OXN3006) continued throughout the 52 weeks of the extension study as BFI scores continued to reduce over time. In the subgroup of subjects receiving a total daily dose of more than 80/40 mg OXN PR per day on more than 7 consecutive days the results indicate comparability with the results for the total exposure safety population.

Date of the Report: 10 NOV 2009