## 2. SYNOPSIS

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| **Name of Company:** Mundipharma Research GmbH & Co. KG | INDIVIDUAL STUDY TABLE | (For National Authority Use Only) |
| **Name of Finished Product:** | Referring to Part IV of the Dossier | |
| **Name of Active Ingredient:** Oxycodone/naloxone combination | Volume: Page: | |

**Title of the Study:** An open-label extension study (OXN3001S) following on from a randomised, double-blind, parallel-group, multicentre study (OXN3001) to demonstrate improvement in symptoms of constipation in subjects with non-malignant pain taking oxycodone equivalent of ≥20 mg/day and ≤50 mg/day as oxycodone/naloxone prolonged-release compared to subjects taking oxycodone prolonged-release tablets alone.

**Investigator/Centres:**

93 sites: UK 49; Germany 28; Spain 6; Czech Republic 10. 61 of the 93 sites had subjects who enrolled in the Extension Phase (OXN3001S).

**Publication (Reference):** TBA

| **Study Dates:** | **Study Status:** | **Phase of Development:** |
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| 21 Apr 2006 (FPFV) to 25 Apr 2008 (LPLV) | Completed | Phase 3 |

**Objectives:** The objective of OXN3001S was to examine the long-term safety and efficacy of OXN PR in subjects with non-malignant pain.

**Methodology:** OXN3001S was an extension study available to those subjects who completed the Double-blind Phase of OXN3001. The results of the Double-blind Phase are presented in a separate report (OXN3001 CSR - 5 October 2007). The optional Extension Phase (OXN3001S, the results of which are presented in this CSR) assessed the long-term safety of open-label Oxycodone/Naloxone prolonged release tablets (OXN PR) for up to 52 additional weeks. Subjects continued on open-label OXN PR every 12 hours. The starting dose was the effective analgesic dose, based on the Oxycodone PR dose that the subject was on at the end of the Double-blind Phase of OXN3001. Dose titration was permitted at the discretion of the Investigator, including subjects' OXN PR dose, rescue dose and laxative dose. Subjects OXN PR doses could be titrated to a maximum of 80 mg/day. Investigators were allowed to prescribe concomitant therapy, including rescue medication and laxatives, as needed. Oxycodone IR (OxyIR) and study laxatives were provided for the first seven days of the extension.

**Number of Subjects:** 258 Subjects entered the Extension Phase (OXN3001S). 227 Subjects completed the study.

**Indication and Criteria for Inclusion:** Males and females, 18 years of age or older with documented history of moderate to severe nonmalignant pain that required around-the-clock opioid therapy (oxycodone equivalent of ≥20 mg/day and ≤50 mg/day) who had constipation caused or aggravated by an opioid and who were likely to benefit from WHO step III opioid therapy for the duration of the study and who had completed the Double-blind Phase (OXN3001).

**Test Treatment, Dose, and Mode of Administration** Oxycodone/naloxone prolonged-release tablets (OXN) 10/5, 20/10, and 40/20 mg taken orally.

**Duration of Treatment:** Up to 52 weeks.

**Treatment Schedule:** At Visit 9, subjects who met the Extension Phase Entrance Criteria (i.e., had completed the Double-blind Phase) had the option to receive open-label Oxycodone/Naloxone PR for up to 52 additional weeks during the Extension Phase. Dose titration was permitted at the discretion of the Investigator.

**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, Subjective Opiate Withdrawal Scale (SOWS) scores, clinical laboratory results, vital signs, physical examinations, 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.

The primary focus of data summarisation and analysis was on response to OXN in the "total exposure safety population". The "duration of exposure" refers to the total amount of time (days) for which a subject has been taking OXN; this includes time in the extension phase only.

The incidence of adverse events was tabulated. Clinical laboratory results, vital signs, and ECG findings were summarised.

**Results:**

Efficacy: The BFI score continued to improve with OXN PR use. Subjects on Oxycodone/Naloxone PR continued the trend seen in OXN3001, in that the BFI score reduced throughout the Extension Phase. By the end of the Extension Phase the mean (SD) BFI had reduced from 35.6 (27.74) at Visit 9 to 20.6 (24.01) by Visit 15, which is a mean reduction of 15 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 (OXN3001), shows that while all subjects continued to show a reduction in BFI values during the Extension Phase, this reduction was greatest, and was also clinically relevant, in those subjects who switched from Oxycodone PR to Oxycodone/Naloxone PR at the beginning of the extension phase.

At Visit 9, subjects who were taking Oxycodone PR in the Double-blind Phase and who had only just switched to Oxycodone/Naloxone PR, had a mean (SD) BFI score of 42.7 (28.61) compared to those who had been on Oxycodone/Naloxone PR in the Double-blind Phase who had a mean (SD) BFI score of 28.7 (25.15). By Visit 10 of the Extension Phase, which was only 1 week after Visit 9, the BFI score of subjects originally on Oxycodone PR had dropped to a mean (SD) of 26.1 (23.31) which was roughly equal to that of subjects who had also been taking Oxycodone/Naloxone PR in the Double-blind Phase (mean (SD) 26.2 (25.09) at Visit 10). From Visit 10 onwards the scores dropped at roughly similar rates in both groups, culminating at Visit 15 with mean (SD) BFI scores of 22.8 (25.59) in subjects who had originally been taking Oxycodone PR and 18.6 (22.30) in subjects who had originally been taking Oxycodone/Naloxone PR.

Mean 'average pain' scores were very similar at each visit in the Extension Phase; these mean 'average pain' scores were also similar to those seen in the Oxycodone PR and the Oxycodone/Naloxone PR group during the Double-blind Phase, (Mean (SD) Oxycodone PR, 3.7 (1.89); mean (SD) Oxycodone/Naloxone PR, 3.4 (1.84); Total mean (SD), 3.5 (1.87) at Visit 8 of the Double-blind Phase vs Oxycodone/Naloxone PR, 3.1 (1.94) at Visit 15 of the Extension Phase). These results confirm that stable pain control was maintained with Oxycodone/Naloxone PR throughout the duration of the Extension Phase.

Analgesic rescue use was low, throughout the Extension Phase and until the end of the study. For the first week 75.3% of the total subject days were recorded as days where no analgesic rescue intake was required and the mean daily use (mg) was only slightly higher during the first seven days of the Extension Phase (mean (SD) = 2.51mg (4.60mg)) compared with the end of the Double-blind Phase (1.92mg (4.41mg). The mean daily supplemental analgesic use was low (0.4 (0.64)) and similar to that seen at the end of the Double-blind Phase (0.3 (0.55)). After the first week, analgesic use was only recorded as concomitant medication. Concomitant medication records show that opioid analgesics, and other analgesics and antipyretics were used by 83 subjects (32.17%) and 65 subjects (25.19%) respectively, indicating that the majority of subjects were able to control their pain on study medication alone.

**Safety:** 26 subjects experienced a total of 34 serious adverse events, the majority of which were not related to study drug. This number included one death due to necrotising facitis, which was not considered by the Investigator to be related to study drug. 211 subjects (81.8%) experienced adverse events during the extension phase. Of these subjects only 125 (48.4%) experienced related (unlikely to be related, possibly related, probably related or related) adverse events The most common adverse events experienced were infections and infestations and musculoskeletal and connective tissue disorders. The third most common class of adverse events was gastrointestinal disorders (94 subjects (36.4%) experiencing 164 events). There were 40 subjects who experienced constipation (15.5%) and 18 subjects who experienced diarrhoea (7.0%). Overall, only 11.2% (29) of subjects experienced constipation that was classed as possibly, probably or definitely related to study drug and only 2.7% (7) of subjects experienced diarrhoea that was possibly, probably or definitely related to study drug. 2 subjects had adverse events associated with opioid withdrawal, one not related and one possibly related to study drug. However, in general SOWS scores were stable and low throughout the study. The mean values for haematology, blood chemistry and vital signs parameters were within the normal range across the study. ECG changes were infrequent and isolated. No apparent safety concerns of treatment with Oxycodone/Naloxone PR were identified.

**Conclusions:**

Average pain scores remained stable throughout the extension study and analgesic rescue use was low, confirming that analgesic efficacy of Oxycodone/Naloxone PR was maintained in the long term. 81.8% (211) of subjects experienced adverse events but only, 48.4% (125) of these were related (unlikely to be related, possibly related, probably related or related) 26 subjects experienced serious adverse events, the majority of whom (18) experienced serious adverse events that were not related to study medication. There was one death in this study but again this was not related to study medication. Importantly, the incidence of diarrhoea was low and SOWS sumscores were not exacerbated with Oxycodone/Naloxone PR.

This study provides evidence that Oxycodone/Naloxone PR is safe and efficacious for long-term therapy in subjects with non-malignant pain and also demonstrates that the improvement in bowel function seen with Oxycodone/Naloxone PR during the Double-blind Phase (OXN3001) is continued throughout the 52 weeks of the Extension Study as BFI scores continued to reduce over time. Interestingly, when BFI scores were split based on what treatment subjects had been taking during the Double-blind Phase, the BFI scores of those subjects who had originally been on Oxycodone PR were seen to drop rapidly (within a week) when they were switched to Oxycodone/Naloxone PR and thereafter kept at a similar level with those subjects who had been taking Oxycodone/Naloxone PR throughout.

**Date of the Report:** 7 April 2009