2. SYNOPSIS

Name of Company: Mundipharma Research GmbH & Co. KG	INDIVIDUAL STUDY TABLE	(For National Authority Use Only)
Name of Finished Product: **Targin®, Targinact®, Targiniq®**	Referring to Part … of the Dossier	
Name of Active Ingredient: **Oxycodone/Naloxone**	Volume: Page:	

Title of the Study: An open-label extension study (OXN2001S) following from a randomised, double-blind, active-controlled, double-dummy, parallel group study (OXN2001) to determine the safety and efficacy of oxycodone / naloxone prolonged release tablets in subjects with moderate to severe, chronic cancer pain

Investigator: The study was undertaken at 31 sites, Czech Republic: 6, France: 2, Germany: 6, Hungary: 4, Israel: 3, Netherlands: 2, Poland: 5, UK: 3.

Publication (Reference): None

Study Dates:	**Study Status:**	**Phase of Development:**
17-Dec-2007 to 17-Aug-2010	Completed	Phase 2

Objectives:

The overall objective for the extension phase OXN2001S study was to evaluate the long-term safety and efficacy of OXN PR and quality of life in subjects with moderate to severe cancer pain:

- To assess safety parameters following treatment with oxycodone / naloxone (OXN PR)
- To assess subjects' assessment of opioid-induced constipation, constipation symptom severity, impact and bothersomeness based on the Bowel Function Index (BFI),Patient Assessment of Constipation Symptoms (PAC-SYM) and PAC-SYM including bothersomeness questions (PAC-SYM(b))
- To assess efficacy in treatment of moderate to severe chronic cancer pain based on the Brief Pain Inventory – Short Form (BPI-SF)
- To assess health status and quality of life based on the EuroQol EQ-5D and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30).

Methodology:

This was an uncontrolled, open-label study using OXN PR in subjects with moderate to severe, chronic cancer pain. Subjects received open-label OXN PR for up to 24 weeks. Visits 1 – 9 were part of the double-blind phase of the core study OXN2001. Study Visit 9a was the first visit of the extension phase study and typically occurred on the same day as Visit 9. Visits were performed after 1 day (V10), 1 week (V11), 12 weeks (V12) and 24 weeks (V13). Rescue medication (oxycodone immediate release (OxyIR)) and laxative medication (bisacodyl) were supplied for the first 7 days of the extension phase study. Following completion/discontinuation of the study subjects were followed up by telephone for 7 days to collect non-serious adverse events and for 30 days to collect serious adverse events (SAEs).

Number of Subjects:

One hundred and twenty-eight subjects entered the extension phase study OXN2001S; all 128 subjects received study medication. Sixty-eight subjects completed the study. The number of subjects who discontinued (46.9%) are not unexpected bearing in mind the patient population (cancer patients) combined with the long duration of the study.

Indication and Criteria for Inclusion:

Subjects (male and female, 18 years or older) were enrolled into the double-blind study OXN2001 if they were suffering with moderate to severe chronic cancer pain that required around-the-clock opioid therapy and they had constipation, secondary to opioid treatment. Subjects who completed study OXN2001 were eligible to enter the extension phase OXN2001S study (subjects who completed OXN2001 may not have had on-going opioid induced constipation on entry to OXN2001S). In addition, subjects who had discontinued from OXN2001 due to constipation were also eligible to enter OXN2001S. All subjects had to comply with all relevant core study screening inclusion and exclusion criteria and be willing and able to participate in all aspects of the OXN2001S study, including use of open-label OXN PR, completion of subjective evaluations, attending scheduled clinic visits, and compliance with protocol requirements.

Test Treatment, Dose, and Mode of Administration:

OXN PR tablets 5/2.5, 10/5, 20/10, and 40/20 mg, oral, every 12 hours.

Reference Treatment, Dose, and Mode of Administration:

None.

Duration of Treatment:

Up to 24 weeks.

Treatment Schedule:

During the study, subjects received open-label OXN PR. At Visit 9a subjects entering the study on a dose up to and including 80 mg/day OxyPR/OXN PR were switched directly to OXN PR. Those subjects on 90 mg/day, 100 mg/day, 110 mg/day or 120 mg/day OxyPR/OXN PR were switched to OXN PR in a stepwise manner based on the dose of oxycodone PR/day they were receiving at the end of OXN2001 (the core study double-blind treatment phase) or at the time point of discontinuation due to constipation.

Dose titration was permitted at the discretion of the Investigator up to a maximum of 120/60 mg/day.

Criteria for Evaluation:

Efficacy:

- BFI
- Laxative use
- Modified BPI Short Form (BPI-SF)
- Amount of analgesic rescue medication (first 7 days only)
- PAC-SYM and PAC-SYM (b)
- Quality of Life (QoL) parameters.

Safety:

Safety was determined by assessment 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 SAEs e.g. hospitalisation for surgery/diagnostic procedures, life threatening status, or death caused by the underlying malignant disease, were not reported as SAEs if they were undoubtedly unrelated to study medication.

Statistical Methods:
All analyses were performed on the Safety Population which was defined as subjects who received at least one dose of study medication during the extension study.

All efficacy and safety variables were summarised descriptively.

All continuous variables were summarised using the following descriptive statistics: n, mean, standard deviation (SD), median, minimum and maximum. The frequency and percentage of observed levels were reported for all categorical measures.

In general, all data were listed, sorted by subject and, when appropriate, by study day within subject.

Adverse events (AEs) were classified into standardised medical terminology from the verbatim description (Investigator term) using MedDRA (version 10.1). AEs were presented by preferred term nested within System Organ Class. The incidence of AEs was tabulated.

Results:
One hundred and twenty-eight subjects entered the extension phase study of which 46.9% were female and 53.1% male. The mean (SD) age of subjects was 62.48 (10.33) years.

Efficacy:
Subjects entering the extension phase study had a mean (SD) BFI baseline (data collected at Visit 9 of the core study) value of 42.21 (27.12) (LOCF) (i.e. total value from the core study double-blind treatment groups OxyPR and OXN PR). Whereas subjects previously treated with OXN PR had a mean at Visit 9/baseline value of 38.08 (26.94). Throughout the extension phase study the total mean BFI value was comparable to that of Visit 9/baseline OXN PR (Visit 12 38.20 (27.77); Visit 13 38.90 (27.47)) indicating that the effect of OXN on bowel function is maintained over the longer term. Results of the PAC-SYM were in accordance with those of the BFI (mean total symptom scores 11.40 (Visit 12) and 12.14 (Visit 13), mean frequency of symptom scores 1.46 (Visit 12) and 1.71 (Visit 13) and were further supported by the PAC-SYM (b) results. From day 7 of the extension phase until the end of the study 12.5% of subjects used laxative on a regular basis.

The mean (SD) modified BPI-SF pain scores (LOCF) were low and stable over the 24-week study (3.52 (1.90) at Visit 9 and 3.63 (2.19) at end of study Visit 13) which indicated good analgesic efficacy during long-term treatment with OXN PR. These values were analogous to those observed during the respective double-blind phase in both treatment arms from the core study full analysis population (OXN PR and OxyPR) indicating a comparable analgesic efficacy of OXN PR and OxyPR. Analgesic rescue medication (Oxy IR) was only provided for the first week of the extension phase study, after which use was recorded as concomitant medication. The need for analgesic rescue medication was low in regards to frequency of use and dose: the average number of times per day that pain rescue medication was used was 0.73 (SD 0.88) (range 0 – 3.9 times a day) and the average number of capsules used per day was 1.10 (1.50) and ranged from 0 to 8.1 capsules. Rescue medication use during this period was comparable to that noted in the double-blind phase from the core study full analysis population (less than one intake per day). Relative to the QoL mean scores observed at the end of the double–blind phase in the full analysis population of the core study, the QoL mean values observed in the extension phase for this sub-set of patients generally showed similar or better average scores.

Safety:

An overall summary of AEs is presented below. One hundred and twenty (93.8%) subjects reported a total of 615 AEs during the course of the extension phase study. Thirty-six subjects (28.1%) had AEs classed as related (definitely, probably, possibly or unlikely related) by Investigators. The number of related SAEs was low (4 events in 4 subjects (3.1%)). The Sponsor assessed two additional SAEs in one subject as 'related'. In addition, six subjects had SAEs after the 7 day follow up period but within the 30 day follow up period for SAEs. All of these SAEs were unrelated and all, with the exception of 2 cases of urinary tract infection, were due to disease progression or events related to disease progression.

Thirty-eight subjects (29.7%) discontinued the study due to AEs. A total of 28 subjects (21.9%) died during the extension phase of the study. Of these 28 deaths, 24 were due to disease progression or events related to disease progression, the remaining deaths were due to sepsis (subject 20301), worsening dyspnoea (subject 50204), lung embolism (subject 50401) and cardiac arrest (subject 80707). With the exception of one death (worsening of dyspnoea) recorded as 'unlikely' to be related, all deaths were recorded as 'unrelated' to study medication.

Summary of Adverse Events: Safety Population

Category	**Oxycodone/Naloxone (N=128) n (%)**
Number of AEs	615
Number of Subjects with AEs	120 (93.8)
Number of related AEs [(a)]	74
Number of Subjects with related AEs [(a)]	36 (28.1)
Number of severe AEs	77
Number of Subjects with severe AEs	49 (38.3)
Number of SAEs	120
Number of Subjects with SAEs	59 (46.1)
Number of related SAEs [(a)]	4
Number of Subjects with related SAEs [(a)]	4 (3.1)

AE: Adverse Event. N: Number of subjects in population, n: Number of subjects with available data, %: Percentage based on N.
[(a)] as assessed by the investigator

Conclusions:

- This study provides supportive evidence for the long-term efficacy and safety of OXN PR in the treatment of subjects with moderate to severe chronic cancer pain.

- The average pain scores based on the modified BPI-SF were low and stable over the 24-week study which indicated a good analgesic efficacy during long-term treatment with OXN PR in subjects with moderate to severe chronic cancer pain that was comparable to the 4-week core study in which subjects had been treated with either OxyPR or OXN PR. This conclusion was further supported by the low analgesic rescue medication use which showed that switching from OxyPR/OXN PR in the double-blind phase to OXN PR in the extension phase did not lead to an increase in Oxy IR rescue medication use.

- The improvement in bowel function demonstrated by the core study was maintained during the 24-week extension phase study.
- The number of related SAEs was low.

- The safety profile and death rate were as expected for this patient population, in accordance with the safety profile of opioid analgesics and shows that OXN PR is safe and well tolerated in this advanced cancer patient population.

In summary, OXN PR maintained the improved bowel function and level of analgesic efficacy that was noted in the 4-week core study over the longer term.

Date of the Report: 18-Aug-2011