2. SYNOPSIS

Name of Sponsor/Company Mundipharma Oy **Name of Finished Product**: Targiniq™ **Name of Active Ingredient:** Oxycodone/naloxone combination	Individual Study Table Referring to Part of the Dossier: Volume: Page:	(For National Authority Use only):
Title of Study:	A randomised, double-blind, parallel group multicentre study to demonstrate non-inferiority of the analgesic efficacy of oxycodone/naloxone 10/5 or 20/10 mg prolonged release tablets (OXN PR) BID compared to oxycodone 10 or 20 mg prolonged release tablets (OXY PR) BID in subjects with postoperative pain after knee arthroplasty.	
Investigators:	Five Investigators	
Study centre(s):	Five centres in Finland: Kuopio University Hospital; University Hospital of Turku; Hospital for joint replacement, Tampere; Hospital of Oulaskangas, Oulainen; and Central Hospital of Pori.	
Publication (reference):	None at the time of this report.	
Studied Period (years):	Phase of Development: IV	
Study Initiation Date: (Date of first enrolment):	25 March 2010	
Study Completion Date: (Date of last completed):	17 October 2010	

Objectives:

Primary objective:

- To demonstrate that treatment with OXN PR tablets is non-inferior to treatment with OXY PR tablets in terms of analgesic efficacy in patients with postoperative pain after knee arthroplasty based on average pain intensity scores at rest. Dosing commenced 1 hour (±30 minutes) before the end of postoperative epidural analgesia. Subjects rated their pain intensity on an 11-point numerical rating scale (NRS) of 0-10, immediately before the first dose and 1 hour after each dose of study medication for 5 doses (2.5 days).

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Secondary objectives:

- To evaluate the safety of OXN PR compared with OXY PR in terms of adverse events (AEs), physical examination, vital signs (supine blood pressure, heart rate and respiratory rate) and 12-lead electrocardiogram (ECG).
- To compare the use of rescue analgesia between the OXN PR and OXY PR groups during the double-blind treatment phase.
- To compare average dynamic pain intensities (11-point NRS) between the OXN PR and OXY PR groups during the double-blind treatment phase.
- To compare current and worst pain intensities at rest and dynamic (11-point NRS) between the OXN PR and OXY PR groups during the double-blind treatment phase.

Exploratory objectives:

- To compare laxative intake between the OXN PR and OXY PR groups during the double-blind treatment phase.

Methodology:

This is a double-blind, multicentre, parallel group study. The study was conducted in two phases: a pre-randomisation phase, comprising a screening period (Days –18 to –2) and a run-in period (Days –2 to 1); followed by a 5-dose treatment phase (Days 1, 2 and 3).

Pre-randomisation phase:

Screening period:

Subjects were screened over a period of up to 14 days. The screening visit was performed during the preoperative evaluation of the subject, which was usually within 2 weeks before planned surgery, but could be performed as late as on the morning of the surgery. A visit window of ±2 days was permitted. Subjects who gave written informed consent were assessed for their eligibility for the study. Screening evaluations included medical history, record of concomitant medications, physical examination, vital signs (supine blood pressure, heart rate and respiratory rate), routine laboratory tests (including liver function tests and creatinine), and 12-lead ECG.

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Run-in period:

The run-in period was the time during which the subject received post-surgical epidural analgesia (approximately 48 hours).

Double-blind phase:

On the morning of the second postoperative day (approximately 48 hours after surgery), the subjects' eligibility for the study was checked. Eligible subjects were randomised to twice daily dosing with OXN PR 10/5 mg or 20/10 mg or OXY PR 10 or 20 mg.

Subjects assessed their pain at rest and on moving (dynamic), immediately before the first dose of study medication on Day 1, then twice daily, 1 hour after each dose of study medication on Days 1 and 2, and in the morning after dosing on Day 3, using an NRS from 0–10. Rescue medication (oxycodone instant release [OXY IR] 5 mg capsules, OxyNorm) was given if the subject's score on the NRS was ≥4. Vital signs, use of rescue medication, laxative use, AEs and concomitant medications were assessed throughout the double-blind phase.

The double-blind phase ended after the fifth pain assessment (in the morning of Day 3, end of treatment). The end of treatment assessments included vital signs, physical examination and 12-lead ECG. However, the physical examination could be performed up to 2 days after the last dose of study medication if the subject remained in hospital. Subjects who withdrew from the study, or who were discharged from hospital, before the fifth dose of study medication had the end of treatment assessments performed if possible.

Number of Subjects (Planned and Analysed):

It was planned that 134 subjects would be randomised: 67 subjects to each treatment group. Assuming a drop-out rate of 20%, it was estimated that 160 subjects would be enrolled in the study to achieve 134 randomised subjects.

At the end of the study, 153 subjects were enrolled and 137 subjects were randomised:
70 subjects were randomised to the OXN PR group and 67 subjects were randomised to the OXY PR group.

Diagnosis and Main Criteria for Inclusion:

Eligible subjects gave written, informed consent, were of either sex, aged 18-75 years inclusive, with body mass index (BMI) 18–35 kg/m^2 inclusive. Subjects had a confirmed diagnosis of osteoarthritis of the knee and had surgical arthroplasty planned on one knee that

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was expected to be followed by postoperative epidural analgesia for approximately 48 hours, and daily opioid treatment after epidural analgesia for 2.5 days. Women of childbearing potential had a negative pregnancy test at screening and used an adequate and highly effective method of contraception throughout the study.

Subjects were excluded from the study if they had used opioids, or had taken laxatives to treat constipation, within 3 months before the start of the screening period; or had taken another investigational medicinal product within 30 days before the start of the screening period; had a history of chronic constipation, concurrent rheumatoid arthritis, or had planned bilateral arthroplasty or revision knee arthroplasty. Other reasons for exclusion are encompassed by a history or presence of other medical conditions that might have caused a safety hazard to the subjects or that could have confounded the interpretation of the results.

Test Product, Dose and Mode of Administration, Batch Number: The test product was oxycodone/naloxone 20/10 mg or 10/5 mg prolonged release (OXN PR) combination tablets for oral administration.

The dose of test medication was determined by the age of the subject. Subjects aged <65 years took the higher strength of study medication (OXN PR 20/10 mg) and subjects aged ≥65 years took the lower strength (OXN PR 10/5 mg). Once selected, the subject remained on that dose for the duration of the double-blind treatment period. The randomisation procedure was stratified by age group to ensure balance between the treatment groups for each strength of double-blind study medication.

A double-dummy technique was used to achieve double-blinding.

Batch number of OXN PR 20/10 mg active tablets: PN3343

Batch number of OXN PR 10/5 mg active tablets: PN3390

Batch number of OXN PR 20/10 mg placebo tablets: PN3229

Batch number of OXN PR 10/5 mg placebo tablets: PN3228

Duration of Treatment: Treatment with double-blind study medication commenced 1 hour (±30 minutes) before the end of epidural analgesia and continued for 5 doses, i.e. 2.5 days. The first day of dosing with study medication was Day 1.

Reference Therapy, Dose and Mode of Administration, Batch Number: The reference product was oxycodone 20 mg or 10 mg prolonged release (OXY PR) tablets for oral

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administration. Subjects aged <65 years took the higher strength of study medication (OXY PR 20 mg) and subjects aged ≥65 years took the lower strength (OXY PR 5 mg).

Batch number of OXY PR 20 mg active tablets: PN3354

Batch number of OXY PR 10 mg active tablets: PN3355

Batch number of OXY PR 20 mg placebo tablets: PN3218

Batch number of OXY PR 10 mg placebo tablets: PN3217

Criteria for Evaluation:

Efficacy:

Primary efficacy variable:

- The primary efficacy variable was the 24-hour pain intensity score at rest, on an NRS from 0-10, assessed 1 hour after dosing on Day 1, Day 2 and Day 3 (morning only).

Secondary efficacy variables:

- Use of rescue analgesia.
- 24-hour dynamic pain intensity scores.
- Current and worst pain intensities at rest and dynamic.

Exploratory efficacy variables:

- Use of laxative medication.

Safety:

Safety was assessed by the documentation of AEs, vital signs (supine blood pressure, heart rate and respiratory rate), physical examination, and 12-lead ECG.

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Statistical Methods:

For the primary efficacy variable (24-hour pain intensity score at rest assessed 1 hour after dosing on Day 1 [evening only], Day 2 and Day 3), absolute changes from baseline were analysed on the Per Protocol (PP) data using a mixed-model repeated measures analysis of covariance (RMANCOVA). Factors for site, age group, time point, treatment group, and pain results immediately before the first dose were incorporated into the statistical model as baseline covariate. The non-inferiority boundary was set to 1.0, i.e. non-inferiority could be concluded if the upper 95% confidence limit of the treatment difference (OXN PR to OXY PR) did not exceed 1.0. Analysis of the Full Analysis (FA) population was supportive.

For the pain score secondary efficacy variables, a similar statistical model was applied as for the primary endpoint but the focus was on estimation of the treatment differences. A Kaplan-Meier estimate for cumulative survival without rescue medication was calculated.

A Kaplan-Meier estimate for cumulative survival without laxative use was calculated.

Summary statistics were produced for each of the efficacy and safety variables.

SUMMARY – CONCLUSIONS:

Of the 137 subjects randomized, 54 subjects (39.4%) were male and 83 subjects (60.6%) were female. Mean age was 64 years (range 38 to 75 years). All of the subjects were Caucasian.

Efficacy Results:

Primary Efficacy Variable

At baseline, mean pain intensity at rest in the PP population was slightly higher in the OXN PR group (3.4) compared with the OXY PR group (3.1). Mean pain intensities gradually decreased from the evening assessment on Day 1 until the last pain assessment on the morning of Day 3. The change from baseline to Day 3 was slightly higher in the OXN PR group (-1.7) compared with the OXY PR group (-1.3).

Overall, 24-hour average pain intensity at rest decreased by 1.2 (95% CI: -1.5 to -0.9) in the OXN PR group and by 1.1 (95% CI: -1.4 to -0.8) in the OXY PR group (Table S1). The mean difference between the groups in the change from baseline in 24-hour average pain intensity at rest was -0.1 (95% CI: -0.5 to 0.3). Since the upper limit of the 95% CI was below 1, it can be concluded that OXN PR is non-inferior to OXY PR.

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In the FA population, the upper limit of the 95% CI for the mean difference between the groups in the change in 24-hour average pain intensity at rest was below 1. Therefore, the conclusion that OXN PR is non-inferior to OXY PR is supported.

Table S1: Analysis of the Primary Efficacy Variable

Pain intensity parameter	OXN PR	OXY PR	OXN PR – OXY PR
24-hour average pain intensity at rest (PP population)	-1.2 (-1.5 to -0.9) (N=59)	-1.1 (-1.4 to -0.8) (N=62)	-0.1 (-0.5 to -0.3)
24-hour average pain intensity at rest (FA population)	-1.2 (-1.5 to -0.9) (N=70)	-1.1 (-1.4 to -0.9) (N=67)	-0.0 (-0.4 to 0.4)

The analysis of the secondary efficacy variables is summarised in Table S2. At baseline, mean average pain intensity scores for each variable were similar in the two groups, or were slightly higher in the OXN PR group compared with the OXY PR group. Mean average pain intensities gradually decreased from the evening assessment on Day 1 until the last pain assessment on the morning of Day 3. The changes from baseline to Day 3 were similar in the two groups or were slightly higher in the OXN PR group compared with the OXY PR group.

Overall, pain intensity decreased in both groups and the mean differences between the groups in the changes from baseline were small and not significant.

Table S2: Analysis of Secondary Efficacy Variables

Pain intensity parameter	OXN PR N=70	OXY PR N=67	OXN PR – OXY PR
24-hour average dynamic	-1.1 (-1.5 to -0.8)	-1.2 (-1.5 to -0.9)	0.1 (-0.4 to 0.5)
Worst at rest	-1.7 (-2.1 to -1.3)	-1.8 (-2.2 to -1.4)	0.1 (-0.5 to 0.6)
Worst dynamic	-0.9 (-1.3 to -0.6)	-1.0 (-1.4 to -0.7)	0.1 (-0.4 to 0.6)
Current at rest	-1.0 (-1.2 to -0.7)	-1.2 (-1.4 to -0.9)	0.2 (-0.1 to 0.5)
Current dynamic	-1.2 (-1.5 to -0.8)	-1.3 (-1.6 to -0.9)	0.1 (-0.4 to 0.6)

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In the FA population, 55 subjects (78.6%) in the OXN PR group and 49 subjects (73.1%) in the OXY PR group took OXY IR rescue medication during the double-blind treatment phase. The mean dose of rescue medication was 21 mg in the OXN PR group and 16 mg in the OXY PR group. The median time to the start rescue medication was 6.0 hours (95% CI: 3.8 to 9.3) in the OXN PR group and 8.8 hours (95% CI: 5.9 to 18.5) in OXY PR group.

In the FA population, 24 subjects (34.3%) in the OXN PR group and 24 subjects (35.8%) in the OXY PR group took laxatives during the double-blind treatment phase. The median time to the start laxative use was 60.0 hours in both groups.

Safety Results:

The incidence of treatment emergent AEs was similar in the two treatment groups: 52 AEs were reported by 41 subjects (58.6%) in the OXN PR group, and 48 AEs were reported by 37 subjects (55.2%) in the OXY PR group.

The most frequently reported AEs were constipation (26 subjects [37.1%] in the OXN PR group and 22 subjects [32.8%] in the OXY PR group) followed by nausea (7 subjects [10.0%] in the OXN PR group and 8 subjects [11.9%] in the OXY PR group) and vomiting (4 subjects [5.7%] in the OXN PR group and 3 subjects [4.5%] in the OXY PR group). All of the treatment emergent AEs were mild or moderate.

There were no treatment emergent SAEs. However, 2 randomised subjects experienced SAEs that commenced before study medication started; both of these subjects were randomised into the OXN PR group while the SAEs were ongoing. Three subjects had treatment emergent AEs that led to discontinuation of study medication: 2 subjects (2.9%) in the OXN PR group discontinued study medication because of dizziness (10/5 mg cohort) and vomiting (20/10 mg cohort), and 1 subject (1.5%) in the OXY PR group discontinued study medication because of fatigue (20 mg cohort).

There were no abnormal clinically significant abnormalities in vital signs or ECG.

Conclusions:

- Oxycodone/naloxone prolonged release tablets (10/5 mg and 20/10 mg) are non-inferior to oxycodone prolonged release tablets (10 mg and 20 mg) in terms of 24-hour average pain intensity at rest in subjects with postoperative pain after knee arthroplasty.
- Oxycodone/naloxone prolonged release tablets (10/5 mg and 20/10 mg) showed similar

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efficacy to oxycodone prolonged release tablets (10 mg and 20 mg) in terms of 24-hour average dynamic pain intensity, worst pain intensity at rest and on moving (dynamic), and current pain intensity at rest and on moving (dynamic).

- Younger subjects (<65 years) taking oxycodone/naloxone 20/10 mg tablets were more likely to require rescue analgesia than older subjects (≥65 years) and all subjects taking oxycodone alone.
- The use of laxatives was similar with both treatments.
- No safety concerns were raised in this study.

Date of Report: 26 January 2011