2. SYNOPSIS

Name of Sponsor: 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 Combination	Volume: Page:	

Protocol No.: OXN2503	**EudraCT/IND No.:** 2009-0018118-21

Title of the Study: An exploratory, randomised, double-blind, placebo-controlled, parallel group, pilot study to assess the analgesic efficacy of oxycodone/naloxone prolonged release tablets (OXN PR) compared to placebo in opioid-naïve subjects suffering from severe pain due to Bladder Pain Syndrome (BPS).

Investigators: A total of 32 centres were initiated in five countries: Czech Republic (8 sites), Germany (7 sites), Hungary (6 sites), Poland (7 sites), and United Kingdom (4 sites). Twenty of these sites (5 in the Czech Republic, 3 in Germany, 2 in Hungary, 7 in Poland, 3 in the United Kingdom) enrolled subjects. A list of the participating sites will be attached to this document.

Publication (Reference): None

Study Dates:	**Study Status:**	**Phase of Development:**
6-Jan-2012 to 25-Mar-2013	Completed	Phase 2

Objectives:

Objective of main interest:

To estimate the subjects' average pain over the last 24 hours assessed at each study visit during treatment with OXN PR compared with placebo as measured by the Pain Intensity Scale (NRS 0 – 10).

Further Objectives:

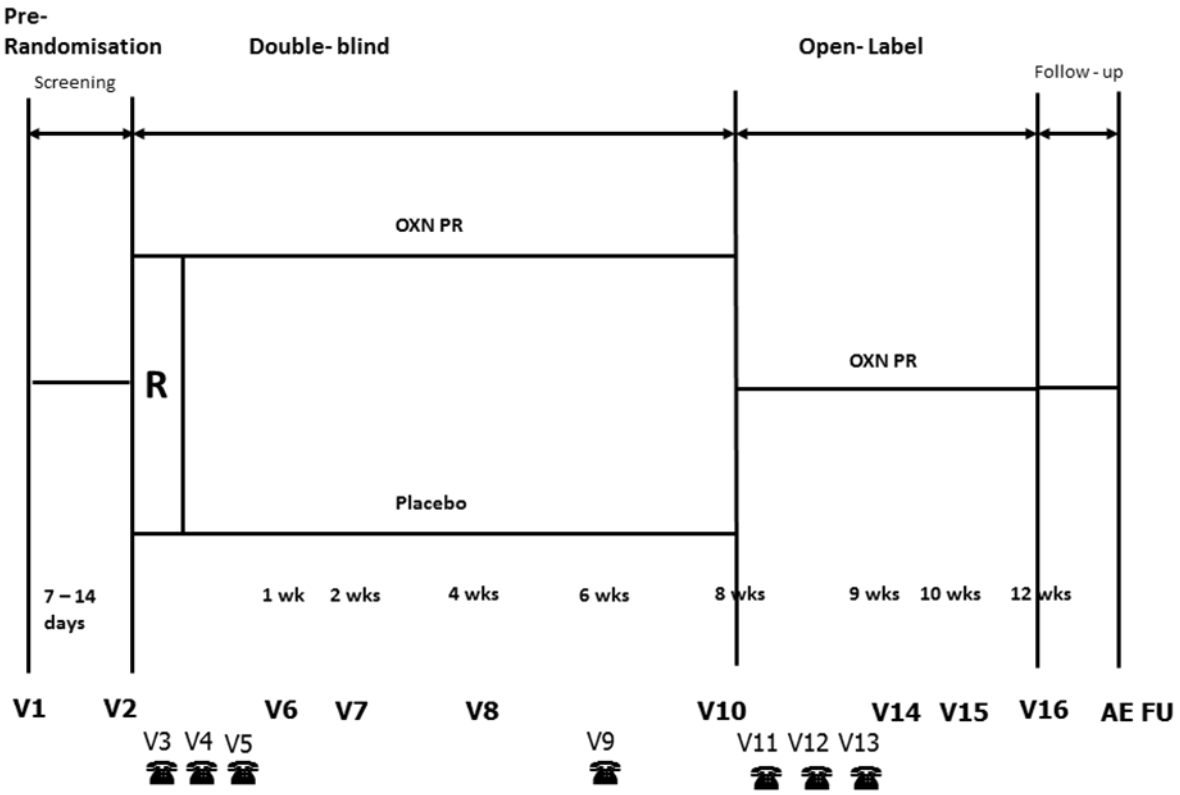
- To assess the frequency of pain rescue medication intake.
- To assess BPI-SF at each clinic visit during treatment with study medication.
- To assess the efficacy based on the O'Leary-Sant Interstitial Cystitis Symptom Index (ICSI) score/ O'Leary-Sant Interstitial Cystitis Problem Index (ICPI) score.
- To assess overall health based on the SF-36 v2.
- To assess micturition (volume and time) based on 24 hours patient diary assessing 2 days in the last week prior to visits 6, 8, 10 and 16.
- To assess urinary urgency using the Patients' Perception of Intensity of Urgency Scale (PPIUS).

Methodology: This was a randomised, double-blind, placebo-controlled, parallel group pilot study in adult female opioid-naïve subjects suffering from severe pain due BPS.

This study was composed of three phases: a Pre-randomisation Phase, a Double-blind Phase and an Open-label Phase.

- In the Pre-randomisation Phase subjects were assessed for their eligibility for treatment. No study medication was given in this phase
- In the Double-blind Phase subjects were randomized in a 1:1 ratio to either OXN PR or placebo. OXN PR or matching placebo were given as add-on therapy. Subjects could be titrated from a starting dose of OXN 5/2.5 mg PR twice daily to a maximum daily dose of OXN 20/10 mg PR twice daily. Treatment duration was 8 weeks.
- The Open-label Phase was designed to treat all subjects with OXN PR and prepare them for an appropriate post-study BPS pain therapy. All subjects would start the Open-label Phase with OXN 5/2.5 mg PR twice daily and could be up-titrated up to a maximum daily dose of OXN 20/10 mg PR twice daily for up to 4 weeks.

Study Design Graphic:



R= Randomisation

Number of Subjects: It was planned to randomise 70 subjects in order to have a total of 60 evaluable subjects (completion of visits 1 – 7 as a minimum).

A total of 68 subjects was screened, and 60 were randomised, of whom 32 were in the OXN PR group and 28 in the placebo group. Of the randomised subjects, 52 (86.7%) completed treatment, 26 in each group. The primary reason for discontinuation of 8 (13.3%) subjects (6 in the OXN PR group and 2 in the placebo group) were AEs (4 OXN PR, 1 placebo) and lack of therapeutic effect (2 OXN PR, 1 placebo). The Full Analysis Population comprised 59 subjects (31 OXN PR, 28 placebo), the per protocol population of 36 subjects (17 OXN PR, 19 placebo). Of the subjects who had completed or discontinued the Double-Blind Phase, 53 subjects continued into the Open-Label Phase, of whom 50 completed treatment and 3 discontinued due to AEs.

Indication and Criteria for Inclusion:

Female subjects, 18 years or older, who were not pregnant and not lactating were included in the study. The subjects had to have a history of severe pain due to BPS for at least 6 months. The pain score on the 0-10 Numeric Rating Scale (NRS) had to be >5. At Czech sites the pain score had to be >7. The BPS diagnosis for subjects at Czech sites had to be confirmed by cystoscopic examination and a histopathology evaluation after biopsy at least 4 weeks prior to the screening visit. At Hungarian sites, an additional check by a pain specialist had to be performed to confirm that subjects were likely to benefit from WHO step III opioid therapy.
All subjects had to have experienced complaints of suprapubic pain related to bladder filling, in the absence of proven urinary infection or other obvious pathology. These complaints had to include scores of ≥ 8 on the ICSI and ICPI, a score of >0 on each of the 4 questions on the ICSI and ICPI, an average of ≥ 8 voids per day and an average of ≥ 2 voids at night (nocturia) within the last month.
The subject's treatment of pain due to BPS had to be insufficient based on clinical judgement, and there had to be a documented history of attempts to optimize the treatment of pain due to BPS.

Subjects were not eligible for enrolment in the study if they had

- previously received ibuprofen (Ibu) regularly for treatment of BPS pain without demonstrating any relevant analgesic effect,
- received opioid containing medication in the last 6 months, naloxone ≤ 30 days prior to the Screening or ibuprofen during the last 2 weeks on a regular basis,
- a history of, or existing peptic ulceration that would place them at risk upon exposure to ibuprofen or that may have confounded the analysis and/or interpretation of the study results,
- suffered from documented confusable diseases for bladder pain syndrome,
- chronic or intermittent pain requiring opioid analgesics that resulted from pain conditions other than BPS,
- received a botulinum toxin injection in the bladder wall within the last 6 months prior to the Screening visit,
- received a hydrodistension within the last 4 months prior to the Screening visit or
- a cystoscopic evaluation within 4 weeks prior to the Screening visit.

To enter the Double-Blind Phase, subjects had to continue to comply with Screening Inclusion/Exclusion criteria and continue to have the severe pain score during the last 7 days prior to visit 2. Subjects had to have an average of ≥ 8 voids per day and an average of ≥ 2 voids (nocturia) at night for at least 2 periods of 24 hours during the Screening Period. Subjects were not to have any indication for current acute bacterial cystitis based on urinalysis at visit 2.

Test Treatment, Dose, and Mode of Administration:

Investigational Drug (Double-blind and Open-label Phase):

Investigational Drug	**Dosage Form / Mode of administration**	**Unit Strength**	**Dosing Frequency**	**Batch No./ Manufacturer's batch No**
Oxycodone / naloxone prolonged-release (OXN PR)	Tablets / oral	5/2.5 mg, 10/5 mg, 20/10 mg oxycodone / naloxone combination	q12h	PN3482/150922 PN3692/161049 PN3689/162721 PN3483/150924 PN3620/158212 PN3693/159019 PN3485/150916 PN3694/160645 PN3729/165389

Reference Treatment, Dose, and Mode of Administration:

Reference Drug (Double-blind Phase):

Reference Drug	Dosage Form / Mode of administration	Unit Strength	Dosing Frequency	Batch No./ Manufacturer's batch No
Matching placebo for Oxycodone / naloxone prolonged-release (matching placebo)	Tablets / oral	5/2.5 mg, 10/5 mg, 20/10 mg oxycodone / naloxone combination	q12h	PN3639/146875 PN3491/151461 PN3392/145935 PN3493/151463 PN3495/151465

Concomitant Medication Including Rescue:

Non-investigational medicinal products (NIMPs) Double-blind Phase:

Rescue Medication (pain)	Dosage Form / Mode of Administration	Unit Strength	Dosing Frequency	Batch No./ Manufacturer's batch No
Ibuprofen (Ibu)	Tablets / oral	400 mg	PRN 400 mg/use	PN3711/LK11411

Ibu was the only pain rescue medication allowed during the Double-blind Phase. It could be dosed no sooner than every 4 hours as needed. An analgesic rescue medication dose was defined as 400 mg of Ibu (1 tablet). The maximum total daily dose was 1200 mg (3 tablets). During the Double-blind Phase, subjects who were on the maximum daily dose of Investigational Medicinal Product (IMP) (OXN 40/20 mg PR or placebo), who on > 3 days per week required > 2 rescue medication doses per day were allowed to enter the Open-label Phase of the study prematurely.

NIMPs Open-label Phase:

Rescue Medication (pain)	Dosage Form/ Mode of Administration	Unit Strength	Dosing Frequency	Batch No./ Manufacturer's batch No
Oxycodone immediate-release (OxyIR)	Capsules / oral	5 mg	PRN 5 mg/use	PN3695/162092

Oxycodone immediate-release (OxyIR) was the only pain rescue medication allowed during the Open-label Phase. The maximum daily dose of OxyIR was 30 mg. A single dose of OxyIR was defined as 5 mg which could be taken up to 6 times per day. It could be dosed no sooner than every 4 hours as needed. When a subject was downtitrated during the last 2 weeks of the Open-label Phase, they should not have taken more than 3 capsules of OxyIR per week for the treatment of breakthrough pain. If subjects required > 2 rescue intakes on ≥ 2 consecutive days, or consistently (i.e. > 3 days per week) required > 2 rescue medication intakes per day, the study medication had to be uptitrated. Subjects who were on the maximum daily dose of IMP (OXN 40/20 mg PR), who on > 3 days per week required > 2 rescue medication doses per day had to be discontinued from the study.

Concomitant medication

All medications not prohibited by the protocol and considered necessary for the subject's welfare might have been administered and/or continued under the supervision of the Investigator.
Concomitant therapies, including over-the-counter medications, that were ongoing as of the date of informed consent were to be kept constant until study completion.
Occasional use of non-opioid analgesics (e.g. for the treatment of headache) were permitted throughout the study. Concomitant medications containing opioids were not to be prescribed. The subject's pre-study BPS treatment was to remain stable throughout the Double-blind and Open-label Phase.
A proton-pump inhibitor could be prescribed during the Double-blind Phase as treatment and prophylaxis of non-steroidal anti-inflammatory drugs -associated benign gastric ulcers, duodenal ulcers and gastroduodenal erosions in patients with a previous history of gastroduodenal lesions.

Duration of Treatment: The total expected duration of a study subject's participation in the study was 14 – 15 weeks with 12 weeks of treatment in the Double-blind and Open-label Phases, as follows:

Pre-randomisation Phase: 7-14 days (no study treatment).

Double-blind Phase: 8 weeks.

Open-label Phase: 4 weeks.

Safety Follow up: 7 days (no study treatment)

Treatment Schedule:

During the Double-blind Phase, subjects received OXN PR or placebo twice daily for 8 weeks. The starting dose was OXN 5/2.5 mg PR twice daily. The following doses were allowed for twice daily use: OXN 5/2.5 mg PR, OXN 10/5 mg PR, OXN 15/7.5 mg PR (given as OXN 10/5 mg PR + OXN 5/2.5 mg PR) and OXN 20/10 mg PR twice daily.

During the Open-label Phase, subjects received OXN PR twice daily for 4 weeks. All subjects started the Open-label Phase on a dose of OXN 5/2.5 mg PR twice daily.

During the Double-blind and Open-label Phase uptitration to a maximum dose of OXN 40/20 mg PR per day was possible if pain was not sufficiently controlled An uptitration could be conducted on every 2^{nd} – 3^{rd} day up to the maximum daily dose (OXN 40/20 mg PR). The increase of the daily dose should have usually been done only by one dose level. If the Investigator felt that the increase of the daily dose by one dose level was not sufficient the increase could also be done by a maximum of two dosing levels. In the Open-label Phase, uptitration was permitted during the first 2 weeks only.

Criteria for Evaluation:

Efficacy Assessments:

Objective of main interest:

- To estimate the subjects' average pain over the last 24 hours assessed at each study visit during treatment with OXN PR compared with placebo as measured by the Pain Intensity Scale (NRS 0 – 10).

Further Objectives:

- To assess the frequency of pain rescue medication intake.
- To assess the Brief Pain Inventory – Short Form (BPI-SF) at each clinic visit during treatment with study medication.
- To assess the efficacy based on the O'Leary-Sant Interstitial Cystitis Symptom Index (ICSI) score/ O'Leary-Sant Interstitial Cystitis Problem Index (ICPI) score.
- To assess overall health based on the SF-36 v2.
- To assess micturition (volume and time) based on 24 hours patient diary assessing 2 days in the last week prior to visits 6, 8, 10 and 16.
- To assess urinary urgency using the Patients' Perception of Intensity of Urgency Scale (PPIUS).

Safety: Safety was assessed by documentation of adverse events (AEs), clinical laboratory results, vital signs, physical examinations, and electrocardiograms (ECGs) and recorded on the standard Case Report Form (CRF) pages and Serious Adverse Event (SAE) data form.

Statistical Methods:

Analysis Populations:

Enrolled: All subjects who provided informed consent.
Randomised Population: The randomised population was defined as all randomised subjects.
Full-Analysis (FA): The full analysis population was defined as all subjects who were randomised and have received at least one dose of study medication during the DB Phase and who have at least visit 7 assessment of the efficacy variable of main interest
Per-Protocol (PP): The per-protocol population was defined as subjects who received at least one dose of study medication during the Double-blind Phase and who sufficiently complied with the study protocol. Subjects without major protocol deviations were be regarded as sufficiently complying with the study protocol. Major protocol violations were agreed at the Determination of Subject Evaluability Assessment (DOSEA) meeting prior to database lock.
The PP population was not analysed for efficacy if this population consisted of more than 95% or less than 50% of the full analysis population. The analysis of the PP population was intended to provide supportive evidence of the analysis of the full analysis population.
Double-blind Phase Safety (DB SF): Subjects who received at least one dose of Double-Blind IMP and had at least one safety assessment after that dose.
Open-label Phase Safety (OL SF): Subjects who received at least one dose of Open-Label IMP and had at least one safety assessment after that dose.

Efficacy Analyses: All efficacy variables were summarised by treatment group and visit.
Summary statistics for data from the Open-Label Phase were summarised in separate tabulations to the Double-Blind Phase data.
For all efficacy analyses the FA population was the primary analysis population. The PP population was used for sensitivity analyses. The Open-Label Safety population was used for analyses during the Open-Label Phase.
The default summary statistics for continuous variables was the number of observations (n), mean, standard deviation (SD), median, minimum (min) and maximum (max). Mean and median were presented to one more decimal place than the raw value, SD was presented to two more decimal places than the raw value, the minimum and maximum values were presented with the same decimal precision as the raw value.
For categorical variables, the number (n) and percentage (%) of patients with non-missing data per category were the default summary presentation, and where appropriate and present, the number of missing values as a "Missing" category. Percentage values were presented to one decimal place, for example, 52.3%. The denominator used for percentage calculations was specified in a footnote to the tables for clarification.

Interim Analyses: Not applicable.

Post-hoc Analyses: Post-hoc subgroup analyses of the average pain ICSI/ICPI, PPIUS, and BPI-SF results were done for the following subgroups:

- Subjects with BPS treatment at the Screening visit versus subjects without ongoing BPS treatment.
- By country.
- Subjects with previous surgical procedures (i.e. conditions of the Surgical and medical procedures SOC in current conditions or medical history) versus subjects without such procedures.

Safety Analyses: AEs, clinical laboratory test results, vital signs, ECG findings and vigilance impairment findings were descriptively summarised and reported separately for each Safety population.

Sample Size Rationale: Although this was an exploratory pilot study for hypothesis generation, statistical sample size estimation has been performed for the change to baseline in the average pain over the last 24 hours. With an assumed standard deviation of 2, a sample size of 31 completing evaluable subjects enabled for a two-sided 95% confidence limit whose width should not exceed 2 on the average. Taking into account early drop-outs, approximately 70 subjects in total needed to be randomised in order to have a total of 60 evaluable subjects.

Results

All subjects were female and Caucasian. The age ranged from 22 to 82 years, with a mean age of 56.1 years at study start. In the open-label phase the mean age was 54.4 years. There were no clinically important differences between the treatment groups in subject demographic/baseline characteristics.

Efficacy:

Pain scores decreased throughout the study in both treatment groups, and in the open-label phase. In the double-blind phase there was a trend for a greater improvement in the OXN PR group in all pain scores, and statistical significance between the groups was reached for several observations in the PP population. The pain decrease from the beginning to the end of the open-label phase was significant in the 24 hour average pain scores as well as the BPI-SF subscales.

Whilst in the FA population there was only a small difference between the two treatments in average pain scores in the last 24 hours, the difference in the PP population was statistically significant after 1 week. Subjects with ongoing BPS therapy at screening showed a greater decrease in pain than the total population, and also a greater decrease than subjects in the placebo group. In the sub-analysis of 24h pain scores by country the same decrease in pain scores in the OXN PR group was observed in all countries except Poland.

Compared to other OXN PR pain studies, in which mean 24-hour pain scores in the OXN PR group at the end of the double blind phase were 3.98 (OXN3401) or 3.4 (OXN3001), respectively, the mean pain score of 5.0 at the end of the double blind phase of this study seems high. However, a comparable pain score of 3.8 was reached after another 4 weeks at the end of the open-label phase. Considering the higher mean pain score at the beginning of this study (7.3 at baseline in the OXN PR group), compared to the baseline pain scores of 5.75 and 5.6 in the OXN PR groups of OXN3401 and OXN3001, respectively, the overall pain decrease over the 12 weeks of double-blind and open-label phase was greater than in OXN3401 and OXN3001, which examined the effect of OXN PR in low back pain.

This pain decrease was confirmed by the ICSI/ICPI scores, and the pain severity and pain interference assessments in the BPI-SF scale, where the same trend could be observed, with a greater difference between the treatment groups, but no statistically significant difference in the FA population. The difference between treatment groups at week 8 was statistically significant for both scores in the PP population (ICSI: p=0.019, 95% CI: -7.45, -0.72; ICPI: p=0.019, 95% CI: -5.96, -0.59). The total intake of rescue medication was also clearly higher in the placebo group at week 8, in addition a greater need for uptitration and concomitant use of analgesics was observed in the placebo group.

The SF-36 showed an improvement in the quality of life for subjects taking part in this study. Though there was a strong placebo effect in every subscale, subjects taking OXN PR showed greater improvements than subjects in the placebo group in the role physical, bodily pain, general health, vitality, and social functioning subscales, as well as the reported health transition. The positive trend was consistently found in the FA as well as the PP population. The SF-36 ratings continued to improve in the open-label phase, with a statistically significant improvement in every subscale between the beginning and the end of the open-label phase.

While improvements in almost all micturition parameters could be observed in both treatment groups, the improvements were greater in the OXN PR group, with a decrease in the frequency and volume, particularly the frequency and volume of urgent micturition and nocturnal micturition. In the PP population, the differences between the OXN group and the placebo group reached statistical significance for overall (24h) urgency-related mean frequency at week 8 (p=0.036; CI: -9.84, -0.37) and week 8 last observation carried forward (LOCF) (p=0.038; 95% CI: -8.02, -0.24), nocturnal urgency- related mean frequency at week 8 (p=0.029; 95% CI: -6.52, -0.38) and week 8 LOCF (p=0.026; 95% CI: -5.34, -0.37) overall total urgency-related volume at week 8 LOCF (p= 0.038; 95% CI: -1965.45, -57.43), overall mean urgency related volume at week 1 (p= 0.047; 95% CI: 0.29, 49.48) and approached statistical significance in daytime mean frequency at week 8 (p=0.051; 95% CI: -2.84, 0.01). Improvements continued in the open-label phase, particularly for those subjects who had received placebo in the double-blind phase, and who showed significant improvements with the intake of OXN PR in the open-label phase with regards to frequency, urgency-related frequency, total volume, and urgency-related volume. This result was confirmed by the PPIUS assessment, where more subjects in the OXN PR group reported improvements than in the placebo group. The results indicate that OXN might increase bladder capacity and reduce urgency and therefore positively influence the normalisation of bladder function. Generally a remarkable placebo effect could be seen. There was a trend for greater improvements in the OXN PR group for all parameters (pain, micturition, quality of life). This trend was particularly pronounced in the PP population where statistically significant differences for some parameters at some time points were observed.

Safety:

- In the double-blind phase 38 (63.3%) subjects experienced 110 AEs. In the OXN PR group 19 (59.4%) subjects experienced 52 AEs and in the placebo group 19 (67.9%) subjects experienced 58 AEs. In the open-label phase 30 (56.6%) subjects experienced 69 AEs. In the open-label phase there were more AEs after the switch from placebo than after the switch from OXN PR.
- 79 AEs in 29 (48.3%) subjects were treatment-related (i.e. unlikely, possible, probably or definitely related to IMP) in the double blind phase, of which 37 AEs in 14 (43.8%) subjects occurred in the OXN PR group and 42 AEs in 15 (53.6%) subjects occurred in the placebo group. In the open-label phase 46 AEs in 19 subjects (35.8%) were treatment-related.
- Most AEs were mild or moderate in severity in both treatment phases.
- Seven subjects – 3 in the placebo and 4 in the OXN PR group – discontinued due to AEs in the double-blind phase, and another 3 subjects discontinued in the open-label phase. The rates of discontinuations due to AEs (11.7% subjects in the double-blind and 11.5% subjects in the open-label phase) were low for an opioid study.
- No subjects died in the course of the study (double-blind and open-label phase). Three SAEs occurred in 3 subjects, all of them in the double-blind phase and none of them were related to IMP. One of the SAEs occurred in the OXN PR group and 2 in the placebo group.
- The most frequently reported AEs in the double-blind phase were constipation, nausea, dizziness, somnolence and vomiting. Except for nausea, they were all reported more frequently in the placebo group. The difference in constipation was particularly high with 6 (21.4%) subjects in the placebo group compared to only 2 (6.3%) subjects in the OXN PR group reporting this event.
- In the open-label phase, dizziness, constipation, nausea and somnolence were the most frequently reported events, though due to the shorter duration, event rates were lower than in the double-blind phase.
- Though some abnormal values were observed in both treatment groups, there was no trend for changes in vital signs or laboratory values in any direction.
- No ECG abnormalities were observed.

Conclusions:

BPS is a complex syndrome, in which pain is only one out of many symptoms that impair the life of patients. Simple pain scales are not sensitive enough to assess all aspects of this multi-facetted disease. Although all efficacy parameters (pain, micturition, quality of life) improved throughout the study in both treatment groups, the average pain over 24 hours did not seem to differ between the OXN PR and placebo group in the FA population. However, the diverse assessment tools in their entirety, that were assessing pain and its interference with daily life, micturition with its most troubling aspects of urgency and night time micturition, and quality of life show a clear trend in favour of OXN PR. In the pain assessments, the trend was clearest in the mean/median of the BPI-SF and the impact of pain on daily function assessment of the BPI-SF. In the micturition assessments OXN PR showed greater improvements in the frequency and volume, particularly in urgency micturition and night time micturition. The trend was more pronounced in the PP than the FA population for all efficacy assessments, indicating a greater benefit for patients who closely followed the recommended treatment regimen. Patients with BPS treatment at screening also had a greater benefit from OXN PR treatment than patients without such treatment. Further improvements in all efficacy parameters were observed in the open-label phase, in which all subjects received OXN PR.

OXN PR was well tolerated and no safety issues were identified. Subjects in the OXN PR group had slightly lower numbers and incidences of AEs, related AEs, severe AEs and SAEs than subjects in the placebo group. In particular, there were fewer cases of gastrointestinal AEs, and slightly less constipation in subjects in the OXN PR group, which is reassuring in this patient population with increased abdominal sensitivity. Though more subjects in the open-label phase experienced AEs after a switch from placebo than after a switch from OXN PR, the AEs they experienced did not point to a safety issue. Laboratory values, vital signs and ECGs were also comparable between the OXN PR and placebo group.

Whilst placebo effects in efficacy could also be observed in other studies with OXN PR (e.g. OXN2502), the number and incidence of AEs and related AEs was always notably lower with placebo than with an opioid. The negation of this difference, with subjects in the placebo group experiencing even slightly more AEs in nearly every category in this study is surprising. This may indicate a positive effect of OXN PR on more than just the pain aspect of the BPS complex of symptoms, which even outweighs the adverse effects patients experience with a strong opioid.

Date of the Report: 17-Mar-2014