SYNOPSIS

Name of Sponsor: Mundipharma Research GmbH & Co. KG	INDIVIDUAL STUDY TABLE	(For National Authority Use Only)
Name of Finished Product: Oxycodone/naloxone prolonged release tablets (OXN 5/2.5; 10/5, 20/10, and 40/20 mg PR)	Referring to Part … of the Dossier	
Name of Active Ingredient: Oxycodone/naloxone combination	Volume: Page:	

Protocol No.: OXN3502S	**EudraCT/IND No.:** 2009-011107-23

Title of the Study: An open-label single-arm (OXN PR) extension phase (OXN3502S) of a randomised, double-blind, placebo-controlled, parallel-group, multicenter study (OXN3502) to demonstrate improvement of symptoms of RLS in subjects with moderate to severe idiopathic RLS with daytime symptoms who take oxycodone/naloxone prolonged release (OXN PR) compared to subjects taking placebo

Investigator: The study took place in Germany, Austria, Spain and Sweden.

Publication (Reference): None

Study Dates:	**Study Status:**	**Phase of Development:**
03-Aug-2010 to 10-Mar-2012	Completed	Phase 3

Objectives: The objectives for the open-label Extension Phase were:

- Proportion of subjects with Augmentation according to the Max-Planck Institute (MPI) Criteria, 2007 (MPI Consensus conference) during OXN PR treatment (Expert's/Investigator's assessment).
- Assessment of severity of augmentation (ASRS) during OXN PR treatment.
- Tolerability and safety of long-term treatment with OXN PR.
- Long-term efficacy of OXN PR during the open-label Extension Phase according to the Double-blind Phase:

Methodology: Details of the respective randomized, Double-blind, placebo-controlled, parallel-group, multicentre study are provided in the OXN302 clinical study report (Protocol OXN302 09-Oct-2009, Final Version 1.0).

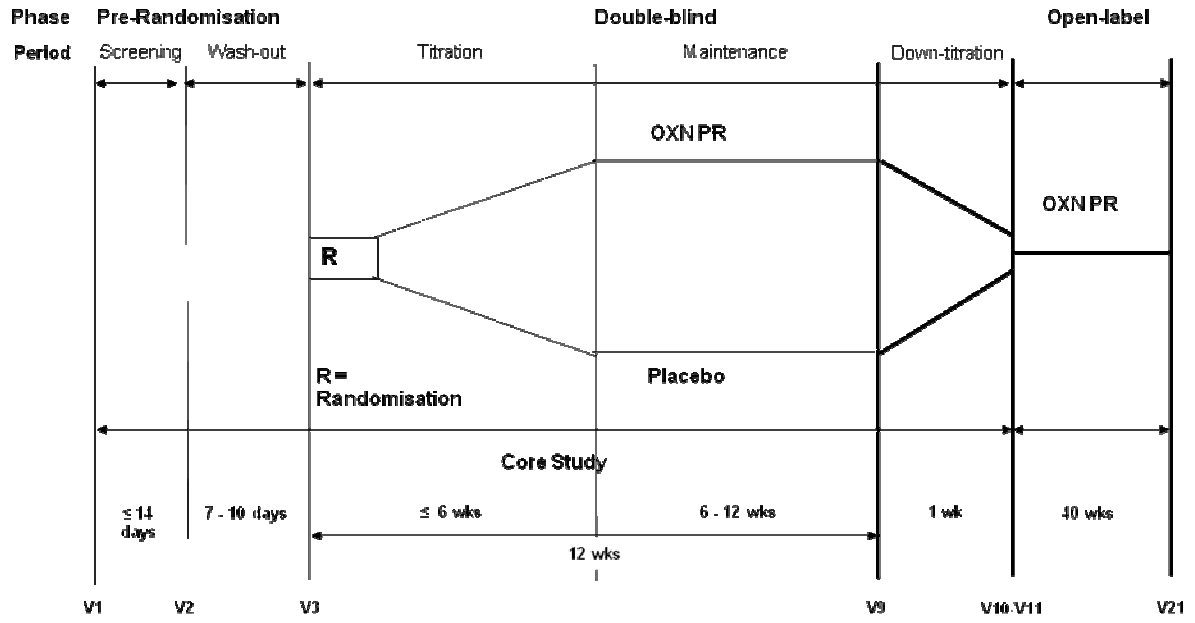
This Extension Phase was a 40-week open-label study. At the end of the Maintenance Period (Visit 9) of the Double-blind Phase the study medication (OXN PR or placebo) was tapered down over a period of 1 week to OXN5/2.5 mg PR or the respective placebo. At Visit 11 (typically occurred on the same day as the end of the 1 week Down-titration Period of the Double-blind Phase (i.e. Visit 10)), subjects who qualified for the entry into the open-label Extension Phase started on OXN5/2.5 mg twice daily. During the open-label Extension Phase a titration on a daily basis up to a daily dose of OXN40/20 mg twice daily was possible but not mandatory; some patients remained at the initial dose. Dose adjustments were allowed throughout the whole 40 weeks to achieve the dose with the individually optimised ratio between efficacy and tolerability. During the first week of the Extension Phase subjects were contacted on a regular basis (every 2-3 days) by telephone to assess Adverse Events (AEs), general restless leg syndrome (RLS)-related health status, vigilance and need for up titration.

If a subject needed to be up titrated, an 'unscheduled visit'/scheduled visit was completed. The assessments at these visits included the documentation of the pulse rate, blood pressure, respiration rate and vigilance (e.g. somnolence). If up titration was done at a scheduled visit, the above-mentioned assessments were performed in addition to the regular visit assessments. If possible up titration (i.e. first intake of higher dose of study medication) and subsequent assessments of blood pressure, pulse rate, respiration rate and vigilance (e.g. somnolence) should have been performed at the study site. In cases where first intake of the higher dose could not be administered at the study site, the first intake was performed by the patient at home. This was closely monitored by the investigator via telephone (i.e. a telephone call was made as soon as possible after intake of higher dose of study medication, and further calls were made if deemed necessary by the investigator). Pulse rate, blood pressure, respiration rate and vigilance (e.g. somnolence) were recorded at

every regular visit following the up titration. Subjects were instructed to report by telephone every change in vigilance (e.g. somnolence) to the investigator.

Subjects were contacted 7 days after the end of the Extension Phase for follow up (AE FU) of any on-going AEs and to record any new AEs that may have occurred.

Study Design Graphic:



Number of Subjects: 197 subjects entered the Extension Phase, which was completed by 157 (79.7%) subjects and 40 (20.3%) subjects discontinued, 21 (10.7%) because of AEs, 11 (5.6%) withdrew voluntarily, 6 (3.0%) because of lack of therapeutic effect, 1 (0.5%) for administrative reasons, and 1 (0.5%) was lost to follow-up.

Indication and Criteria for Inclusion: Full details of the inclusion and exclusion criteria for the Double-blind Phase of the study are provided in the OXN302 study report (Protocol OXN302 09-Oct-2009, Final Version 1.0). In order to enter this Extension Phase, subjects had to continue satisfying Screening Inclusion/Exclusion criteria, had to have completed the Double-blind treatment Phase, and were not suffering from a clinically significant augmentation. Subjects who prematurely discontinued the Double-blind Phase due to lack of therapeutic effect but were treated with study medication for at least 8 weeks were also eligible to enter the Extension Phase.

Test Treatment, Dose, and Mode of Administration:

Test Treatment Open-label Extension Phase:

Study Medication	Dosage Form	Unit Strength	Dosing Frequency	Mode of Administration
Prolonged-release oxycodone/naloxone (OXN PR)	Tablets	5/2.5, 10/5, 20/10, and 40/20 mg OXN PR tablets	q12h	Oral

At Visit 11 (typically occurred on the same day as Visit 10), subjects who qualified for the entry into the open-label Extension Phase started on OXN5/2.5 mg PR twice daily. During the open-label Extension Phase a titration on a daily basis up to a dose of OXN40/20 mg PR twice daily was allowed. Dosing was fixed and symmetrical (5/2.5, 10/5, 15/7.5, 20/10, 25/12.5, 30/15, 35/17.5 and 40/20 mg OXN PR twice daily). OXN PR was taken every 12 hours with or without food with sufficient liquid.

Reference Treatment, Dose, and Mode of Administration: None

Concomitant Medication Including Rescue

All medications not prohibited by the protocol and considered necessary for the subject's welfare may have been administered and/or continued under the supervision of the investigator.

Duration of Treatment: The total duration of open-label treatment during the extension phase was 40 weeks.

Treatment Schedule:

During the Extension Phase, subjects started on OXN5/2.5 mg PR twice daily. A titration on a daily basis up to a daily dose of OXN40/20 mg PR twice daily was allowed, throughout the whole 40 weeks.

Criteria for Evaluation:

Efficacy Assessments

- International Restless Legs Syndrome Study Group Rating Scale (IRLS).
- Clinical Global Impression (CGI).
- Augmentation Severity Rating Scale (ASRS).
- RLS-6-Rating Scale.
- RLS Pain Intensity Scale
- QoL-RLS-Scale.
- MOS sleep scale.

Evaluation of augmentation:

Occurrence of augmentation in individual patients was identified by use of the screening tool for augmentation during study. If indicated, subjects were evaluated for augmentation symptoms using the MPI criteria checklist (Garcia-Borreguero et al., 2007).

Investigators were asked to thoroughly evaluate the presence of augmentation symptoms at each visit during the open-label Extension Phase. A potential augmentation case was suspected if one or more of the following criteria was met:

- In a screening tool for augmentation, a patient indicated worsened severity of symptoms compared to the status at the previous visit.
- Augmentation was diagnosed according to a checklist assessing the MPI criteria checklist for the diagnosis of augmentation.
- Once a potential case of augmentation was suspected by individual investigators, a local augmentation expert called the patient to perform a standardised interview based upon the MPI criteria checklist. There was one local augmentation expert per country who was responsible for all patients from all sites per country. All local augmentation experts discussed the interview outcome with an independent augmentation expert not involved in the conduct of the study. After this discussion, the augmentation case was classified into 'no augmentation', 'MPI criteria present but not clinically relevant augmentation' or 'clinically relevant augmentation'. This statement defined the data for the study endpoint 'rate of augmentation'. Both the local augmentation expert and the independent augmentation expert had access to the data of the individual patients with suspected augmentation. The local augmentation expert did not participate as an investigator in the study.

The decision of the experts was not made available to the investigator.

Safety: Safety was assessed by documentation of adverse events, 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 as well as the CGI tolerability scale.

Statistical Methods:

Analysis Populations:

Extension: The subset of the double-blind safety population that was exposed to OXN PR during the open-label Extension Phase.

Efficacy Analyses:

Efficacy variables were summarised by Double-blind treatment and week. Continuous variables were reported using the following descriptive statistics: n, mean, SD, median, minimum and maximum. Categorical variables were summarised using the number and percentage of subjects in each category. Data were listed, sorted by centre and subject, and when appropriate by week.

Interim Analyses: Not applicable.

Safety Analyses:
Safety was assessed based on AEs, clinical laboratory results, vital signs, physical examinations, and ECGs. Summary statistics of safety variables were produced. These were sorted by week where appropriate. Continuous variables were reported using the following descriptive statistics: n, mean, SD, median, minimum and maximum. Categorical variables were summarised using the number and percentage of subjects in each category.

Sample Size Rationale: Not applicable.

Results: The Extension Population comprised 197 subjects (66 male, 131 female) with a mean age of 61.21 years (range 28 to 84 years). All except one were Caucasian. 101 subjects have treated with OXN PR and 96 had received placebo during the Double-blind Phase.

Efficacy: At the end of the Maintenance Period (Visit 9) of the Double-blind Phase subjects entered a one week Downtitration Period. During this Period all subjects had been tapered down to OXN5/2.5 mg twice daily or respective placebo. The end of the Downtitration Period was the end of the Double-blind Phase (Visit 10), at which subjects had the option to enter the open-label Extension Phase or to terminate the study. The start of the Extension Phase (end of Downtitration Period, V10) will synonymously used in the description of the results as week 1.

IRLS Scale
In the total Extension Population, the overall mean (SD) IRLS score at the end of the Maintenance Period of the Double-Blind Phase was 15.39 (11.18). As expected the mean (SD) IRLS score increased from the end of Maintenance Period to week 1 of the Extension Phase (representing the start of the Extension Phase) due to the design of the study (downtitration). At week 1 the mean (SD) total IRLS score was 22.40 (10.49).The mean (SD) total IRLS scores had declined to 9.46 (7.69) by Week 40 of the Extension Phase.
In subjects of the Extension Population treated with OXN PR during the Double-blind Phase, the overall mean (SD) IRLS score was 12.35 (8.99) at the end of the Maintenance Period of Double-blind treatment, which further declined to 10.65 (8.33) at Week 40 of the Extension Phase. Subjects of the Extension Population given placebo during the Double-blind Phase had a mean (SD) overall IRLS score of 18.58 (12.35) at the respective timepoint, which declined to 8.63 (6.95) by Week 40 of the Extension Phase. This demonstrated a further improvement from moderate to mild in IRLS sum score with long-term treatment with OXN PR compared with the benefit achieved after Double-blind treatment (see Appendix).

RLS-6-Rating
At the end of the Maintenance Period of the Double-blind Phase, the mean (SD) scores in the Extension Population for satisfaction with sleep during the last 7 nights was 4.09 (3.22) overall, 3.15 (2.62) for subjects given OXN PR during the Double-blind Phase and 5.08 (3.50) for subjects given placebo. The respective mean (SD) scores at Week 40 in the Extension Phase were 2.01 (1.96), 2.15 (1.92) and 1.84 (2.01). This showed increasing satisfaction with sleep in response to OXN PR treatment during the Extension Phase over and above that achieved during the Double-blind Phase.

In terms of mean (SD) severity of RLS symptoms during the last 7 nights or days at the end of the Maintenance Period of the Double-blind phase and at Week 40 of the Extension Phase (Extension Population), there were improvements at falling asleep, during the night, during the day at rest and during the day when engaged in activities. The overall mean (SD) score for RLS symptoms at falling asleep decreased from 3.31 (3.28) to 1.46 (1.65), during the night from 3.20 (3.23) to 1.45 (1.68), during the day at rest from 2.77 (2.88) to 1.36 (1.69), and during the day when engaged in activities from 1.33 (2.01) to 0.75 (1.21). The mean (SD) overall score for tiredness or sleepiness during the day decreased from 3.54 (3.09) to 2.22 (2.25).

These results showed a further amelioration of the severity of RLS symptoms while trying to sleep, in the course of the night, at rest during the day, during daily activities, as well as increased satisfaction with sleep and a reduction in daytime sleepiness during treatment with OXN PR in the Extension Phase.

CGI
The CGI has been assessed at 4 weeks (Visit 12), 8 weeks (Visit 13) and 40 weeks (Visit 21) of treatment during the Extension Phase.

The overall mean (SD) severity of illness score (Item 1) decreased from 3.15 (1.62) at Visit 9 (end of Maintenance Period) to 2.45 (1.23) at the end of Extension Phase. The respective median values were 3.0 at Visit 9 and 2.0 at the end of the Extension Phase. This represented an improvement change from mildly ill to borderline, which was already present after 8 weeks of treatment with OXN PR. This improvement was maintained throughout the remaining Extension Phase.

The overall mean (SD) global rating of change of condition (Item 2) decreased from 2.11 (1.26) at Visit 9 (end of Maintenance Period) to 1.56 (0.89) at the end of the Extension Phase. The corresponding median values were 2.0 at Visit 9 and 1.0 at the end of the Extension Phase. This represented a change from much improved to very much improved, which was also already present after 8 weeks of treatment. This improvement was maintained throughout the remaining Extension Phase.

Overall mean (SD) therapeutic effect score decreased from 1.87 (1.17) at Visit 9 (end of Maintenance Period) to 1.36 (0.71) at the end of the Extension Phase (Visit 21), representing the category of marked therapeutic effect. The corresponding median values were 1.0 at Visit 9 and 1.0 at the end of the Extension Phase.

Overall mean (SD) side effect score remained stable, being 1.43 (0.61) at Visit 9 (end of Maintenance Period) and 1.57 (0.77) at the end of the Extension Phase (Visit 21). The corresponding median values were 1.0 at Visit 9 and remained stable throughout the Extension Phase. This represents the a category of none to no significant interference with the patient's functioning.

QoL-RLS Scale
The QoL-RLS scale has been assessed during the Extension Phase twice (week 8 and week 40).

Topic 1 (Effects of RLS Symptoms): The mean (SD) scores for each single question remained stable throughout the Extension Phase. An improvement by one category (slightly to very slightly) in the median of item 1 "To what degree do your RLS symptoms disturb your sleep" was be observed.

Topic 2 (Disturbed Sleep and its Effects): Mean (SD) and median scores for each single question remained stable throughout the Extension Phase.

Topic 3 (Effects of Other Features):
The mean (SD) scores for each single question remained stable throughout the Extension Phase. A slight increase by one category (not at all to very slightly) in the median of item 7 "To what degree do you feel impaired by side effects of your RLS medication" could be observed, however this change is not of clinical relevance.

Topic 4 (your Way of Handling the RLS-Symptoms): The mean (SD) scores for each single question remained stable throughout the Extension Phase.

Topic 5 (At The End – Your Overall QoL): Mean (SD) score improved slightly, while the median scores remained stable throughout the Extension Phase.

MOS Sleep Scale
The mean (SD) score for time taken to go to sleep in the past 4 weeks decreased from 2.49 (1.29) at the end of the Maintenance Period of the Double-blind Phase to 2.10 (1.01) at Week 40 of the Extension Phase, which was within the range of 16 to 30 minutes (Table 14.2.1.6). The mean (SD) number of hours of sleep each night during the past 4 weeks increased from 6.06 (1.59) hours at the end of the Maintenance Period of the Double-blind Phase to 6.58 (1.16) hours at Week 40 of the Extension Phase.

Incidence of Augmentation
In total 28 subjects had potential cases of augmentation based on screening tool for augmentation during the study. However no subject had a confirmed case of augmentation during the 40 weeks of the Extension Phase.

Further parameters:
At the end of the Maintenance Period of the Double-blind Phase mean (SD) pain scores for the total extension population was 3.02 (2.84), which decreased to 1.58 (1.82) at Week 40 of the Extension Phase.
As expected in subjects receiving OXN PR in the Double-blind Phase the rate of subjects with a 50% improvement in IRLS sum score compared to the end of the Maintenance Period was low. In subjects receiving placebo during the Double-blind Phase the rate of subjects having a 50% improvement in IRLS sum score was 16.7% – 28.1% throughout the Extension Phase visits. Comparable results were achieved with the CGI item 2 of "much and very improved" with percentages of 26.0% – 33.3% in those subjects receiving placebo during the respective Double-blind Phase. Around 40% of the population even fulfilled criteria of remitters at week 40.

Safety

The median duration of exposure was 281 days (range: 4 to 297 days). The protocol-planned duration of treatment was 40 weeks (~280 days): 156 (79.2%) of subjects received study medication for at least 271 days.
A total of 150 (76.1%) out of 197 subjects experienced AEs during the 40-week Extension Phase. This was not unexpected in a study involving an active opioid treatment given as long-term treatment. The majority of AEs (approximately 85%) were mild or moderate in nature.

Tab 1. Overall Summary of Adverse Events – Extension Population

	Total (N=197)
Subjects with at least one AE [n(%)]	150 (76.1)
Number of AEs (#)	551
Subjects with at least one related[a] AE [n(%)]	112 (56.9)
Number of related AEs (#)	300
Subjects with at least one severe AE [n(%)]	30 (15.2)
Number of severe AEs (#)	47
Subjects with at least one related[a] severe AE [n(%)]	18 (9.1)
Number of related[a] severe AEs (#)	30
Subjects with at least one SAE [n(%)]	13 (6.6)
Number of SAEs (#)	13
Subjects with at least one related[a] SAE [n(%)]	3 (1.5)
Number of related[a] SAEs (#)	3
Subjects who died [n(%)]	--

Cross Reference: Listing 16.2.7.1, 16.2.7.3, 16.2.7.4, 16.2.7.5, 16.2.7.6, 16.2.7.7, 16.2.7.8
AE: Adverse Event. SAE: Serious Adverse Event. N: Number of subjects in population. n: Number of subjects with data available. #: number of Adverse Events %: Percentage based on N.
Note: A subject may have findings in more than one category.

Treatment-related AEs (i.e. AEs that were unlikely, possibly, probably, or definitely related to study medication) were reported for 112 (56.9%) subjects. A total of 300 out of 551 AEs (54.5%) were considered treatment-related The incidence of drug-related AEs was higher in subjects aged ≤65 years (60.9%) than in those aged >65 years (51.2%), although the incidence of drug-related severe AEs was similar (8.7% versus 9.8%, respectively). These were considered to have occurred by chance and were not clinically relevant.

There was a higher incidence of drug-related AEs in females (58.5%) than in males (53.0%), with a slightly higher incidence of severe drug-related AEs in females (9.9% versus 7.6%). These were considered to have occurred by chance and were not clinically relevant. No subjects died during the Extension Phase. Thirteen (6.6%) subjects experienced 13 SAEs during the Extension Phase, of which three (1.5%) subjects experienced treatment-related SAEs (peripheral arterial occlusive disease, ileus, and subileus). All SAEs had resolved with or without sequelae by the end of the Extension Phase, except for foot deformity in one subject that was on-going at study end but resolved post-study.

Adverse events of special interest included opioid withdrawal syndrome and GI AEs. Two (1.0%) subjects experienced two opioid withdrawal adverse events, both of which were considered treatment-related. Overall, seventy-seven (39.1%) subjects experienced 131 GI AEs during the Extension Phase. Most GI AEs (approximately 95%) were mild or moderate in nature.

Twelve episodes of diarrhoea occurred in 12/197 (6.1%) subjects in total (Table 14.3.2.5.1.1), of which 6 (3.0%) had six episodes considered treatment related and no subjects withdrew from the study because of diarrhoea.
Three patients (1.5%) discontinued study medication because of constipation. Additional therapy was required for constipation in 14/197 (7.1%) patients. No cases of constipation required dose reduction or dose interruption.

Upon request of an Ethics Committee, subjects from the German sites of OXN3502 were assessed 30 days after the end of the open label extension phase, if they had developed psychological or physical dependence (according to the definitions by the British Pain Society). Data for 176 subjects are available (Table 14.3.7, Listings 16.2.9.1 and 16.2.9.2). No subject had experienced psychological dependence. Twelve subjects (6.8%) reported signs of physical dependence, which included sweating, insomnia, agitation, headache, tremor, nausea, restlessness, freezing, circulatory disturbance, shivering attacks, uneasiness, anxiety, weakness, loss of appetite, pollakiuria, depressive mood, inner tension, nervousness, tachycardia, dizziness, sweating at night. In 9 subjects these symptoms occurred after abrupt discontinuation, two subjects experienced symptoms after dose decrease and one subject experienced symptoms after switch to another opioid. In 9 of the 12 subjects the symptoms were moderate; two patients had mild and two had severe symptoms. None of the symptoms was assessed as serious.

Analyses of haematology, blood chemistry and urinalysis did not reveal any clinically notable changes over the Extension Phase compared with the end of the Double-blind Phase. Out of range values were observed for some laboratory parameters, most notably increases from normal to high for glucose (31 subjects, 15.7%), triglycerides (20 subjects, 10.2%), and cholesterol (17 subjects, 8.6%). Markedly abnormal haematology and blood chemistry results were reported with similar frequencies at the end of the Double-blind Phase and at the end of the Extension Phase

There were no clinically notable changes in mean vital signs over the course of the Extension Phase. The incidence of clinically notable vital signs abnormalities was low, with two (1.0%) subjects having high diastolic blood pressure at Week 1 and 1 (0.5%) subject having low diastolic blood pressure at Week 32. Thus, there did not appear to be a safety signal regarding vital signs in the Extension Phase. The incidence of clinically significant ECG results was low. Only one (0.5%) subject had ECG findings at Week 40 of the Extension Phase (ST- and T-wave abnormalities).

Conclusions:
The main aims of the Extension Phase study were to assess the efficacy and long-term safety of OXN PR in subjects with RLS, and the proportion of subjects with augmentation according to the MPI criteria. Subjects were thoroughly evaluated for potential augmentation throughout the Extension Phase, but no augmentation occurred throughout the 40 weeks treatment.
The incidence of AEs was as expected for a study of an opioid analgesic in subjects with RLS. The most frequently reported treatment-related AEs were consistent with the known safety profile of OXN PR. Most AEs (approximately 85%) were of mild or moderate severity. Only two (1.0%) subjects had opioid withdrawal AEs,

one subject each aged ≤65 years and >65 years.

Analysis of haematology, blood chemistry and urinalysis did not reveal any clinically notable changes over the Extension Phase compared with the end of the Double-blind Phase. Markedly abnormal haematology and blood chemistry results were reported with similar frequencies at the end of the Double-blind Phase and at the end of the Extension Phase.

There were no clinically notable changes in mean vital signs over the course of the Extension Phase and the incidence of clinically notable vital signs was low. Thus, there did not appear to be a safety signal regarding vital signs during 40-week treatment of RLS subjects with OXN PR.
Overall, there were no new or unexpected observations relating to safety in this population of subjects with RLS.

There were no primary or secondary efficacy statistical analyses defined during the Extension Phase, although evaluation of efficacy continued to be made. Further improvements in the subjects' condition were noted by the end of the Extension Phase.

The mean (SD) total IRLS scores declined to 9.46 (7.69) by Week 40 of the Extension Phase, demonstrating an improvement to mild RLS severity during long-term treatment with OXN PR.

The results of the RLS-6 scale showed a further amelioration of the severity of RLS symptoms while trying to sleep, in the course of the night, at rest during the day, during daily activities, as well as increased satisfaction with sleep and a reduction in daytime sleepiness during treatment with OXN PR in the Extension Phase.

Subjects exhibited increased satisfaction with sleep in response to OXN PR treatment during the Extension Phase, along with decreased tiredness and sleepiness during the day. Increased alleviation in RLS pain was also noted during the Extension Phase. A marked therapeutic effect of OXN PR was noted, and the incidence of side effects did not significantly affect the subjects' functioning (CGI). Further slight improvements in the subjects QoL were also noted during the Extension phase compared with the end of Double-blind treatment, in terms of beneficial effects on sleep, activities of daily living, mood, and social interactions.

The efficacy results emphasize the effectiveness of OXN PR in the long-term treatment of RLS, showing improvements in the subjects' condition, reduction in the severity of illness, improvements in sleep, reduction in RLS-related pain, and improvements in QoL.

The results from the Extension Phase show that OXN PR is well-tolerated and effective for the long-term (40- week) treatment of patients with moderate to severe RLS under treatment.

Date of the Report: 25-Mar-2013

Appendix

Table 2. Summary of overall IRLS by week – Extension Population

Week	Statistic	Double-blind Treatment				Total (N=197)	
		OXN PR (N=101)		Placebo (N=96)			
		Actual Result	Change to End of Double-blind	Actual Result	Change to End of Double-blind	Actual Result	Change to End of Double-blind
End of Double-Blind	n	101		96		197	
	Mean (SD)	12.35 (8.99)		18.58 (12.35)		15.39 (11.18)	
	Median	10.0		18.0		13.0	
	Min, Max	0, 37		0, 40		0, 40	
Week 1	n	101	101	96	96	197	197
	Mean (SD)	21.95 (9.93)	9.60 (10.08)	22.88 (11.08)	4.29 (9.00)	22.40 (10.49)	7.02 (9.91)
	Median	22.0	9.0	24.5	1.0	24.0	3.0
	Min, Max	0, 40	-7, 33	0, 40	-9, 38	0, 40	-9, 38
Week 4	n	99	99	90	90	189	189
	Mean (SD)	14.31 (8.90)	1.72 (8.27)	13.57 (9.28)	-5.23 (11.05)	13.96 (9.06)	-1.59 (10.27)
	Median	13.0	0.0	12.5	-4.0	13.0	0.0
	Min, Max	0, 37	-29, 28	0, 36	-37, 35	0, 37	-37, 35
Week 8	n	95	95	87	87	182	182
	Mean (SD)	12.59 (8.71)	0.40 (7.33)	11.11 (8.18)	-7.29 (10.61)	11.88 (8.47)	-3.27 (9.81)
	Median	11.0	0.0	11.0	-5.0	11.0	-1.0
	Min, Max	0, 35	-29, 23	0, 40	-35, 11	0, 40	-35, 23
Week 12	n	91	91	85	85	176	176
	Mean (SD)	10.92 (7.67)	-1.11 (7.18)	10.71 (7.39)	-7.35 (10.97)	10.82 (7.51)	-4.13 (9.70)
	Median	10.0	0.0	11.0	-5.0	11.0	-2.0
	Min, Max	0, 33	-37, 15	0, 32	-35, 20	0, 33	-37, 20

Week	Statistic	Double-blind Treatment				Total (N=197)	
		OXN PR (N=101)		Placebo (N=96)			
		Actual Result	Change to End of Double-blind	Actual Result	Change to End of Double-blind	Actual Result	Change to End of Double-blind
Week 16	n	91	91	80	80	171	171
	Mean (SD)	10.49 (7.60)	-1.55 (7.73)	9.61 (7.24)	-8.00 (11.19)	10.08 (7.43)	-4.57 (10.01)
	Median	10.0	0.0	10.0	-5.0	10.0	-2.0
	Min, Max	0, 34	-37, 17	0, 28	-35, 19	0, 34	-37, 19
Week 20	n	87	87	79	79	166	166
	Mean (SD)	10.83 (7.64)	-1.32 (7.78)	9.72 (7.09)	-7.52 (10.91)	10.30 (7.38)	-4.27 (9.87)
	Median	11.0	0.0	10.0	-5.0	10.0	-2.0
	Min, Max	0, 35	-37, 18	0, 30	-35, 18	0, 35	-37, 18
Week 24	n	88	88	77	77	165	165
	Mean (SD)	11.15 (8.56)	-0.66 (8.37)	10.05 (6.84)	-7.09 (12.26)	10.64 (7.80)	-3.66 (10.82)
	Median	10.0	-1.0	10.0	-5.0	10.0	-2.0
	Min, Max	0, 36	-37, 26	0, 30	-35, 27	0, 36	-37, 27
Week 28	n	84	84	73	73	157	157
	Mean (SD)	9.95 (7.98)	-1.58 (7.21)	9.85 (7.42)	-7.48 (12.98)	9.90 (7.70)	-4.32 (10.68)
	Median	10.5	-1.0	9.0	-7.0	10.0	-2.0
	Min, Max	0, 31	-37, 20	0, 34	-35, 30	0, 34	-37, 30
Week 32	n	88	88	75	75	163	163
	Mean (SD)	10.18 (7.65)	-1.56 (6.86)	8.53 (6.81)	-8.52 (11.74)	9.42 (7.30)	-4.76 (10.02)
	Median	10.0	0.0	9.0	-6.0	10.0	-2.0
	Min, Max	0, 30	-37, 17	0, 33	-35, 15	0, 33	-37, 17

Week	Statistic	Double-blind Treatment				Total (N=197)	
		OXN PR (N=101)		Placebo (N=96)			
		Actual Result	Change to End of Double-blind	Actual Result	Change to End of Double-blind	Actual Result	Change to End of Double-blind
Week 36	n	85	85	71	71	156	156
	Mean (SD)	10.25 (8.43)	-1.60 (7.39)	8.52 (6.64)	-7.73 (10.66)	9.46 (7.69)	-4.39 (9.50)
	Median	10.0	-1.0	9.0	-4.0	9.0	-2.0
	Min, Max	0, 36	-37, 16	0, 27	-35, 15	0, 36	-37, 16
Week 40	n	82	82	70	70	152	152
	Mean (SD)	10.65 (8.33)	-1.33 (7.43)	8.63 (6.95)	-8.61 (11.23)	9.72 (7.77)	-4.68 (10.02)
	Median	10.0	-1.0	9.0	-6.5	9.5	-2.0
	Min, Max	0, 30	-37, 20	0, 30	-35, 15	0, 30	-37, 20

Cross Reference: Table 14.2.1.1.1, Listing 16.2.6.3

N: Number of subjects in population. n: Number of subjects with data available.

Total IRLS Sum Score ranging from 0 to 40.