2. SYNOPSIS

Name of Company: 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:	

Title of the Study: A randomised, double-blind, placebo-controlled, parallel-group, multicenter study 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.

Investigators: A total of 69 centres were initiated in four countries: Germany (58 centres), Spain (five centres), Austria (three centres) and Sweden (three centres); 55 of these centres (47 in Germany, three in Spain, three in Austria and two in Sweden) screened subjects.

Publication (Reference): None.

Study Dates:	**Study Status:**	**Phase of Development:**
15 April 2010 to 9 June 2011	Completed	Phase 3

Objectives:

The primary objective for the 12-week Titration-/Maintenance Period was:

- To demonstrate superior efficacy of OXN PR compared to placebo in the improvement of symptom severity of RLS as measured by the International Restless Legs Syndrome Study Group Rating Scale (IRLS scale).

The secondary objectives for the 12-week Titration-/Maintenance Period were:

- Assessment of improvement of severity of RLS in the Clinical Global Impression (CGI) severity scale in subjects taking OXN PR compared to placebo.
- Assessment of change of severity of RLS during the day at rest (RLS-6-Rating Scale) in subjects taking OXN PR compared to placebo.
- Assessment of change of severity of RLS in the further RLS-6-Rating scales (severity at bedtime, during the night, during the day when active, sleep quality, daytime tiredness) in subjects taking OXN PR compared to placebo.
- Assessment of change in numeric rating scale (NRS) for pain in subject's legs or arms (RLS pain) taking OXN PR compared to placebo.
- Assessment of the Responder Rate for subjects with (a) at least 50% improvement in the IRLS scale or (b) ratings of "very much" or "much" improved in the CGI scale 2 "change of condition".
- Assessment of the Remitter Rate (a) IRLS scale 0 or (b) a final IRLS score ≤ 10.
- Assessment of change in disease-specific quality of life (QoL-RLS-Scale).
- Assessment of change in sleep behaviour of subjects with OXN PR compared to placebo using the MOS (Medical Outcome Study) sleep scales.
- Assessment of therapeutic effect (based on CGI item 3).
- Assessment of the Incidence of Augmentation
- Assessment of severity of augmentation (Augmentation Severity Rating Scale [ASRS]).

Methodology: This was a randomised, double-blind, placebo-controlled, parallel-group, multi-centre, Phase 3 study. The study comprised a Pre-randomisation Phase of up to 24 days, a Double-blind Treatment Phase of 13 weeks, and an open-label Extension Phase of 40 weeks.

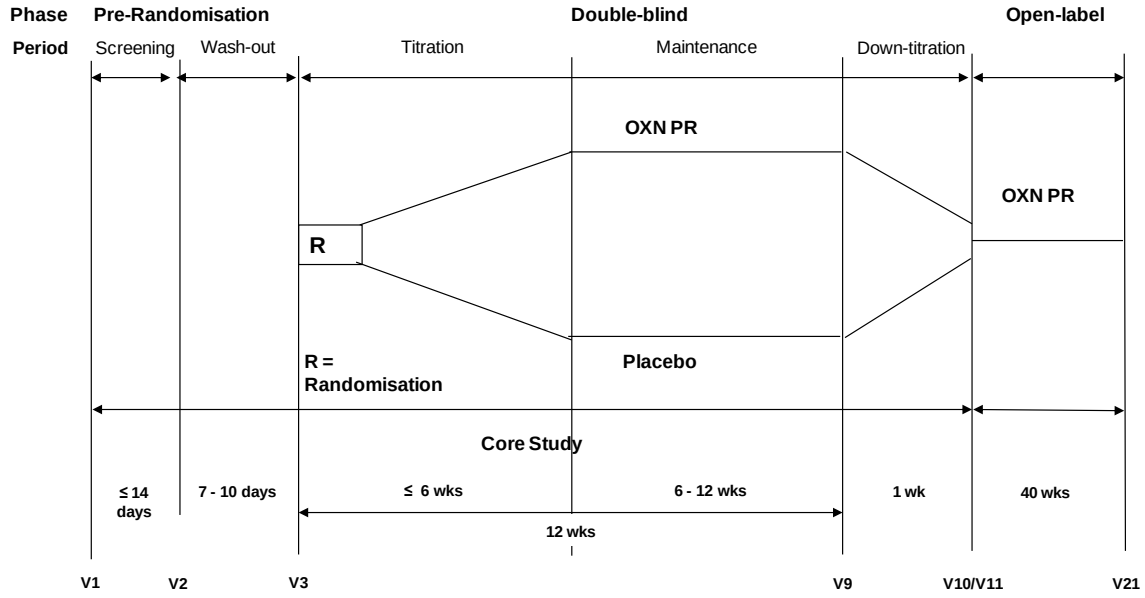
The Pre-randomisation Phase consisted of a Screening Period of up to 14 days, and a Wash-out Period of 7 to 10 days. During the Screening Period, subjects provided informed consent and were evaluated for study eligibility. Eligible subjects underwent a Wash-out Period where their pre-study RLS therapy was stopped or down-titrated, and received no RLS therapy for the last 7 days before randomisation (Day 1).

The Double-blind Phase consisted of a Titration Period of up to 6 weeks, a Maintenance Period of between 6 and 12 weeks, and a Down-Titration Period of 1 week. At the end of the Wash-out Period, subjects who qualified for entry into the Double-blind Phase of the study were randomised to OXN PR or placebo in a 1:1 ratio. The starting dose was either OXN5/2.5 mg PR twice daily or corresponding placebo. Titration (up or down) of the study medication dose was allowed on a weekly basis during the first 6 weeks of the Double-blind Phase, up to a maximum dose of OXN40/20 mg PR twice daily. Throughout the Titration Period, subjects who needed an adjustment of the study medication dose had to attend an unscheduled/scheduled clinic visit. Once the individual dose was determined, subjects continued double-blind treatment with study medication until Week 12. No change in dose was permitted during the Maintenance Period. If a dose adjustment was necessary after Week 6 (e.g., due to intolerability) the subject was withdrawn from the study. At the end of the Maintenance Period, the study medication dose was tapered down to OXN PR 5/2.5 mg or the respective placebo twice daily over a period of 1 week in a double-blind manner. Subjects already on OXN5/2.5 mg PR daily (or the respective placebo) remained on that dose during the Down-Titration Period.

Subjects who qualified for entry into the open-label Extension Phase started on OXN5/2.5 mg PR twice daily. During the open-label Extension Phase dose adjustments were allowed on a daily basis throughout the whole 40 weeks to achieve the dose with the individually optimised ratio between efficacy and tolerability, up to a maximum dose of OXN PR 40/20 mg twice daily. Further details and results from the open-label Extension Phase are provided in a separate clinical study report.

Subjects were contacted 7 days after their last dose of study medication for follow up of any ongoing AEs and to record any new AEs that had occurred. An additional follow-up visit was introduced in Germany by Local Protocol Amendment 1 (12 July 2010). This visit was performed 4 weeks after the end of the open-label Extension Phase and assessed symptoms of physical dependence and the development of psychological dependence.

Study Design Graphic:



Number of Subjects: It was planned to randomise a total of 300 subjects to treatment, to ensure that 266 evaluable subjects were achieved (133 per treatment group). A total of 495 subjects provided written informed consent and were screened, 306 subjects were randomised (OXN PR: 150; placebo: 154; not treated: 2), and 204 subjects completed the study (OXN PR: 107 [71.3%]; placebo: 97 [63.0%]). In the OXN PR group, reasons for discontinuation were AEs (20 subjects), lack of therapeutic effect (10 subjects), subject's choice (seven subjects) and administrative reasons (six subjects). In the placebo group, reasons for discontinuation were lack of therapeutic effect (30 subjects), subject's choice (14 subjects), AEs (10 subjects), administrative reasons (two subjects) and lost to follow-up (one subject).

All 304 randomised and treated subjects were included in the Double-blind Safety population. A total of 276 subjects (132 in the OXN PR group and 144 in the placebo group) were included in the Full Analysis population and 174 subjects (92 in the OXN PR group and 82 in the placebo group) were included in the Per-Protocol population.

Indication and Criteria for Inclusion: Male or female subjects aged 18 years or older, with a diagnosis of RLS (score ≥ 11) according to the "Restless Legs Syndrome Diagnostic Index" (RLS-DI), with a positive response ('yes') to at least one of the following criteria: 7 'positive family history of RLS', 8 'positive response to dopaminergic treatment' and 9 'objective findings of periodic limb movements in polysomnography or actigraphy' OR a negative response ('no') to criterion 10 'usual findings in neurological examination' (Benes & Kohnen, 2008). Subjects had to have had RLS symptoms for at least 6 months, have an IRLS score of ≥ 15 at the screening visit, onset of RLS symptoms before 18:00 on at least 4 days per week and be dissatisfied with any current or previous treatment for RLS. All subjects had received at least one prior RLS therapy that was not sufficiently effective for treating their symptoms. For entry into the Double-blind Phase, subjects had to have an IRLS score of ≥ 21 at randomisation.

Subjects were not eligible for enrolment in the study if they had secondary RLS (e.g. due to iron deficiency anaemia, renal insufficiency, rheumatoid arthritis) or RLS associated with previous or concomitant therapy with dopamine D2 receptor antagonists, butyrophenones, metoclopramide, atypical antipsychotics (e.g. olanzapine), tri- and tetracyclic antidepressants, mianserine, lithium or H_2-blockers (e.g. cimetidine), or due to withdrawal from drugs such as anticonvulsants, benzodiazepines, barbiturates, and other hypnotics. Subjects with history or presence of sleep disturbances caused by sleep apnea syndrome, narcolepsy or myoclonus epilepsy, any disorder whose symptoms could overlap those of RLS (mimics of RLS), acute, clinical augmentation according to MPI criteria and screening tool for augmentation, dementia (e.g. Alzheimer's disease), progressive supranuclear paresis, multisystem atrophy, Huntington's Chorea, amyotrophic lateral sclerosis, Isaac's syndrome, Stiff-Man syndrome, or Gilles de la Tourette's syndrome, or a history or presence of hallucinating or psychotic episodes requiring treatment (including schizophrenia) were also excluded. Subjects were not to have received opioid containing medication (including tilidine, tramadol and codeine) for the treatment of RLS and other disorders (pain) on a regular basis at any time before enrolment. Occasional use for treatment of cough/cold, pain etc was acceptable if the last intake was at least 1 month before enrolment.

Test Treatment, Dose, and Mode of Administration:

Test treatment (Double-blind Phase):

Study Medication	Dosage Form	Unit Strength	Batch No./Manufacturer's batch No.
Prolonged-release oxycodone/naloxone (OXN PR)	Tablets	OXN PR 5/2.5 mg OXN PR10/5 mg OXN PR 20/10 mg OXN PR 40/20 mg oxycodone/naloxone combination	PN3482/150922 PN3483/150924 PN3485/150916 PN3487/150918 and PN3490/150921

Subjects started with a dose of OXN5/2.5 mg PR twice daily. The dose could be titrated up to a maximum daily dose of OXN40/20 mg PR twice daily. Dosing was fixed and symmetrical (5/2.5, 10/5, 20/10, 30/15 and 40/20 mg OXN PR twice daily)

OXN PR tablets were taken orally with sufficient liquid every 12 hours, with or without food.

Reference Treatment, Dose, and Mode of Administration:

Reference Treatment:

Study Medication	Dosage Form	Unit Strength	Batch No./Manufacturer's batch No.
Matched placebo for OXN PR	Tablets	Matching placebos for: OXN PR 5/2.5 mg OXN PR10/5 mg OXN PR 20/10 mg OXN PR 40/20 mg	 PN3491/151461 PN3493/151463 PN3495/151465 PN3498/151468

Subjects started with OXN5/2.5 mg PR matching placebo twice daily. The dose could be titrated up to a maximum daily dose of OXN40/20 mg PR matching placebo twice daily.

Placebo tablets were taken orally with sufficient liquid every 12 hours, with or without food.

Concomitant Medication: All medications not prohibited by the protocol and considered necessary for the subject's welfare were allowed under the supervision of the Investigator. Occasional use of non-opioid analgesics for the treatment of e.g. headache was permitted throughout the study. Concomitant medications containing opioids were not to be prescribed.

Use of drugs likely to influence sleep architecture or motor manifestations during sleep or other central nervous system (CNS) depressants were not permitted from the last week before the randomisation visit onwards. These included levodopa, dopamine agonists, catechol-O-methyl-transferase (COMT) inhibitors, neuroleptics, hypnotics, anxiolytic drugs, benzodiazepines, antidepressants psychostimulatory drugs and anticonvulsants.

Subjects taking pre-study, non-opioid analgesics that were thought to be stable and necessary for the subject's welfare, and were anticipated to remain stable throughout the Double-blind Phase, were permitted to enter the study and continue on their medication under Investigator supervision. Subjects receiving antidepressants (selective serotonin reuptake inhibitor [SSRI] or NARI [noradrenaline reuptake inhibitor]) or anxiolytic drugs for depression or anxiety disorders could enter the study and continue on their medication if their treatment had remained stable for at least 6 months.

Duration of Treatment: The total expected duration of a study subject's participation in the core study was 14 – 16 weeks as follows:

Pre-randomisation Phase: Up to 24 days (Screening Period: up to 14 days, Wash-out Period: 7 - 10 days).

Double-blind Phase: 13 weeks (Titration Period: up to 6 weeks, Maintenance Period: 6 – 12 weeks; Down-titration Period: 1 week)

Treatment Schedule:

During the Screening Period, all subjects continued on their usual RLS medication.

During the Wash-out Period, subjects stopped/downtitrated their pre-study RLS therapy. In the last 7 days prior to randomisation subjects did not receive any RLS therapy.

During the Double-blind Phase, subjects received OXN PR or placebo twice daily for 13 weeks. The starting dose was OXN PR 5/2.5 mg twice daily or corresponding placebo. Titration of the study medication dose was allowed on a weekly basis during the Titration Period (first 6 weeks of the Double-Blind Phase), up to a maximum dose of OXN PR 40/20 mg twice daily. Once the individual dose was determined, subjects continued double-blind treatment with study medication until Week 12 (Maintenance Period). No change in dose was permitted during the Maintenance Period.

Criteria for Evaluation:

Efficacy:

Primary efficacy endpoint:

- Change in severity of RLS as measured by the IRLS scale sum score.

Secondary efficacy endpoints:

- Clinical Global Impression (CGI severity item).
- Clinical Global Impression (CGI change of condition).
- Change in severity of RLS during the day at rest (RLS-6-Rating Scale).
- Change in the further RLS-6-Rating Scales.
- Change in NRS for RLS pain.
- Responder Rates according to IRLS and CGI.
- Remitter Rates according to IRLS.
- Change in disease-specific quality of life (QoL-RLS-Scale).
- Change in sleep behaviour measured by the MOS sleep scale.
- Augmentation assessed by the screening tool for augmentation during study, and, if appropriate, by the MPI criteria checklist during study and clinical expert interview.
- Severity of augmentation (ASRS).

Safety:

- Adverse events (AEs, e.g. learned through spontaneous reports, subject interview)
- Vital signs
- Clinical laboratory test results
- Electrocardiogram (ECG) findings
- CGI tolerability scale

Statistical Methods:

Analysis Populations:

Enrolled: All subjects who provided informed consent.

Full-Analysis: Subjects who were randomised and received at least one dose of study medication during the Double-blind Phase and who had at least a 1 week double-blind assessment of the primary efficacy variable.

Per-Protocol: Subjects who received at least 9 weeks of double-blind treatment and who sufficiently complied with the study protocol. This population was defined in the Statistical Analysis Plan before the unblinding of treatment assignments.

Screening/Wash-out Period Safety: Subjects who had at least one safety assessment during the Screening/Wash-out Period.

Double-Blind Safety: Subjects who received at least one dose of double blind study medication and had at least one safety assessment after that dose.

Primary Efficacy Analysis:

The primary endpoint was compared by mixed model repeated measures (MMRM) analysis of covariance (ANCOVA) with unstructured block diagonal covariance matrix. The model accounted for fixed-factor treatment per visit, baseline IRLS as a fixed covariate, random-effect centre, and subject as random-effect variable. Thereby, data from Visits 1, 2 and 3 were excluded from the analysis model. All early discontinuation data were excluded from the Visit 9/early discontinuation analysis, except for discontinuations due to lack of therapeutic efficacy or augmentation. 95% confidence intervals (CIs) for changes in IRLS (OXN PR - placebo) from baseline to Visits 5, 6, 7, 8 and 9 were calculated to prove superior efficacy of OXN PR versus placebo. No missing value imputation was used.

The hypothesis tests were carried out separately for each of the Maintenance Period assessments beyond Visit 4 in descending order from Visit 10 onwards, as long as the null hypothesis was rejected for all subsequent Maintenance Period assessments. This was an intersection-union test across the various visit outcomes, so that the analysis kept a multiple 5% significance level.

The primary analysis was performed using the Full Analysis population. The primary analysis was repeated using the Per-Protocol population as a robustness assessment, and was also repeated using ANCOVA. Both the MMRM and ANCOVA analyses were replicated using Wilcoxon Rank sum test on change from baseline data.

Secondary Efficacy Analyses:

All secondary parameters were analysed in an exploratory manner separately, using the Full Analysis population. The following endpoints were analysed using Fisher's exact test for 2x2 contingency tables:

- Number of subjects who dropped out from the study
- Number of subjects with 50% improvement in the IRLS sum score
- Number of subjects with ratings of 'very much' or 'much' improved in the CGI scale item 2 (change of condition)
- Number of IRLS remitters.

Any scores (CGI, RLS-6-Rating Scale, Pain-NRS and the QoL measures) were analysed using the same ANCOVA analysis used for the primary efficacy analysis. Visit 8 served as the end of Maintenance Period measure for these endpoints. All secondary ANCOVA analyses were replicated using Wilcoxon Rank sum test on change from baseline data.

Safety Analyses:

AEs, clinical laboratory test results, vital signs, ECG findings and CGI tolerability scale were descriptively summarised. The frequency of AEs and SAEs were reported separately for each Safety population.

Sample Size Rationale: This was a confirmatory study designed to have an overall power of at least 90% in comparing OXN PR to placebo with respect to the IRLS score; the type I error probability was set to 5% two-sided. Assuming a within-subject standard deviation (SD) of 10, a larger improvement under OXN PR by 4 IRLS units (a clinically relevant difference) compared to placebo could be achieved with 266 evaluable subjects, or 133 evaluable subjects per arm. It was planned to randomise a total of approximately 300 subjects to obtain the required number of evaluable subjects, allowing for drop-outs.

The within subject standard deviation of 10 was based upon literature (Trenkwalder et al., 2008c).

Results: The Double-blind Safety population comprised 102 male and 202 female subjects with a mean age of 62 years (range: 28 to 88 years). All subjects except one were Caucasian. All subjects fulfilled RLS diagnostic index and essential criteria of RLS at study entry. The majority of subjects had previously taken levodopa, pramipexole or ropinirole for RLS. There were no notable differences between the treatment groups in subject demographic/baseline characteristics.

Efficacy:

Primary Endpoint:

Superior efficacy of OXN PR versus placebo was demonstrated in the improvement of RLS symptom severity as measured by the IRLS scale. The primary MMRM analysis on the Full Analysis population showed a statistically significantly larger decrease (improvement) in the IRLS sum score in the OXN PR group compared with the placebo group at Visit 9 (Week 12). The treatment difference (OXN PR – placebo) was 8.15, by far exceeding the assumption defining the sample size calculation which was a treatment difference of 4. This is a particularly robust result since the lower 95% CI for the treatment difference at Visit 9 (Week 12) was also greater than the clinically relevant difference of 4 (95% CIs: 5.46, 10.85, p<0.001). A statistically significant treatment difference of a similar magnitude (approximately 8), with a lower 95% CI above 4, was also shown at Visits 5, 6, 7 and 8 (Weeks 2, 3, 4 and 8). A clear effect of OXN PR on RLS symptoms was observed as early as 1 week after the start of treatment, with a decrease in the mean IRLS score of more than 10 points between Visit 3 (baseline) and Visit 4 (Week 1); however, Visit 4 results were not subject to statistical analysis. This was confirmed by the results of the robustness analyses, using a MMRM analysis on the Per-Protocol population, and an ANCOVA and Rank Test analysis on the Full Analysis population.

The mean IRLS sum score at Visit 3 (baseline) was 31.62 (SD: 4.52), therefore on average, subjects had very severe RLS at baseline. The mean IRLS sum score decreased to 11.55 (SD: 8.67) in the OXN PR group and 17.20 (SD: 10.15) in the placebo group at Visit 8 (Week 8). Mean IRLS scores were slightly higher at Visit 9 (Week 12) than Visit 8 (Week 8) in both treatment groups (OXN PR: 15.11 [SD: 10.59], placebo: 22.09 [SD: 12.15]), which is likely due to inclusion of data from discontinuation visits. Additional *post hoc* robustness analyses were performed that analysed results only for subjects who completed all study visits up to Visit 9 (Week 12). These *post hoc* analyses provided very similar results to the planned analyses.

Further summary statistics for the IRLS scale were produced *post hoc* according to the type of prior RLS therapy, and gender. Generally, there was a clearly observable larger decrease in mean IRLS sum scores for OXN PR compared with placebo regardless of prior RLS therapy or gender, with treatment differences for the change from Visit 3 (baseline) to Visit 9 (Week 12) ranging from ~7 to 13.

Secondary Endpoints:

The responder rate (the proportion of subjects with a) at least a 50% improvement in the IRLS sum score from Visit 3 (baseline) to Visit 9 (Week 12) or b) rating of 'very much' or 'much' improved in CGI Item 2 [change of condition]) was statistically significantly higher for the OXN PR group than the placebo group (47.0% vs. 22.9%, p<0.001, Fisher's Exact test). Furthermore, more subjects in the OXN PR group than the placebo group were IRLS remitters (74.2% vs. 26.4%, p<0.001, Fisher's Exact test).

The conclusion of superior efficacy of OXN PR versus placebo in the improvement of RLS symptoms was supported by the results for the further secondary efficacy endpoints. Results of exploratory analyses (ANCOVA and Rank Sum tests) on the secondary efficacy endpoints were statistically significantly more favourable for OXN PR than placebo for almost all endpoints. Note that all secondary endpoints were analysed using the Full Analysis population and the treatment difference refers to OXN PR – placebo.

Clinical Global Impression (CGI)

The results for CGI Items 1, 2 and 3 all showed statistically significantly greater improvement for subjects in the OXN PR group compared with the placebo group. The treatment difference for Item 1 (severity of illness) at Visit 9 was -1.0720 (95% CIs: -1.4631, -0.6808, p<0.001, ANCOVA), the treatment difference for Item 2 (change of condition) at Visit 9 was -0.9304 (95% CIs: -1.2864, -0.5744, p<0.001, ANCOVA), and the treatment difference for Item 3 (therapeutic effect) was -1.0514 (95% CIs: -1.3566, -0.7461, p<0.001, ANCOVA), all in favour of OXN PR. In addition, the number of subjects with ratings of 'very much' or 'much' improved in CGI Item 2 was statistically significantly greater for the OXN PR group (88 subjects [66.7%]) compared with the placebo group (50 subjects [34.7%]) (p<0.001, Fisher's Exact test).

RLS-6-Rating Scale

The results of the RLS-6-Rating scale showed a statistically significant improvement in RLS symptom severity in the OXN PR group compared with the placebo group (95% CIs below zero and p<0.001 for all treatment differences).

RLS Pain Intensity

There was a greater improvement in RLS pain intensity (as measured by the NRS for pain in subjects' arms and legs) in the OXN PR group compared with the placebo group at all post-baseline visits. The mean score decreased from 6.55 (SD: 2.66) at Visit 3 (baseline) to 1.94 (SD: 2.11) in the OXN PR group and 3.42 (SD: 2.91) for the placebo group at Visit 8 (Week 8). There was a slight increase in mean scores at Visit 9/Week 12 (OXN PR: 2.65 [SD: 2.61], placebo: 4.63 [SD: 3.21]). The treatment difference for RLS pain intensity was statistically significant (95% CIs below zero and p<0.001, ANCOVA) at all post-baseline visits analysed (Visits 4, 5, 6, 7 and 8, i.e. Weeks 1, 2, 3, 4 and 8).

QoL-RLS

There was a greater improvement in subjects' quality of life (measured using the QoL-RLS questionnaire) in the OXN PR group compared with the placebo group. This improvement is especially relevant since most subjects were taking their previous treatment at the time of the baseline assessment (Visit 1, screening). A positive effect of treatment with OXN PR was seen at Visit 7 (Week 4) across all five topics of the QoL-RLS, including effects of the RLS symptoms, effects of disturbed sleep, how subject's handle RLS symptoms, effect of pain caused by RLS and overall QoL, with a statistically significant treatment difference (95% CIs below zero and p<0.001, ANCOVA) in favour of OXN PR for all questions except Question 7. Question 7 related to related to side-effects and showed that subjects in the OXN PR group did not feel any more or less affected by their study medication compared with their previous medication for RLS. Visit 9 (Week 12) results were not subject to analysis, however mean and median values for the OXN PR group were similar at Visit 7 and Visit 9, indicating that most of the effect on quality of life occurred over the first 4 weeks of treatment, and that the effect was maintained over 12 weeks of treatment.

Augmentation

Potential augmentation was carefully evaluated by Investigators throughout the study using a series of assessments. Subjects were initially assessed using the Screening Tool for Augmentation, and were further assessed using the MPI criteria checklist if potential augmentation was suspected, with verification of results by Local Augmentation Experts and an Independent Augmentation Expert. There were no confirmed cases of augmentation in either treatment group during the study. Thirty-five subjects had a potential case of augmentation identified using the Screening Tool for Augmentation and were further assessed for augmentation by the Investigator using the MPI criteria checklist; 34 of these subjects were assessed by the Investigator as having no augmentation using the MPI criteria checklist. One subject (179106) was assessed by the Investigator as having augmentation using the MPI criteria checklist; however the Investigator did not consider the augmentation to be clinically significant. The Local Augmentation Expert and Independent Augmentation Expert did not consider augmentation to be present for this subject.

MOS Sleep Scale

There was a greater improvement in sleep quality (measured using the MOS sleep scale) in the OXN PR group compared with the placebo group, with subjects in the OXN PR group falling asleep more quickly, sleeping for longer, experiencing less sleep disturbance and greater sleep adequacy than subjects in the placebo group. The treatment difference for the Sleep Disturbance Scale, Optimal Sleep Scale, Sleep Quantity, Sleep Adequacy and Sleep Problems Index I and II at Visit 7 was statistically significant (95% CIs below zero and p<0.001, ANCOVA). Results for daytime somnolence, waking with shortness of breath/headache and snoring were numerically more favourable for OXN PR than placebo, but the treatment difference for these items did not reach statistical significance.

For all secondary parameters, median values supported the trends observed for mean values, and the results of the Rank Test analyses supported the results of the ANCOVA analyses.

The favourable efficacy results for the OXN PR group were reflected by the drop-out rate, which was lower for the OXN PR group than for the placebo group (22.7% vs. 34.0%, p=0.004, Fisher's Exact test). The discontinuation rate specifically due to lack of efficacy was 6.7% in the OXN PR group and 19.5% in the placebo group. The discontinuation rate due to AEs was 14.7% in the OXN PR group and 6.5% in the placebo group.

Safety: The median duration of treatment was 91.0 days (range: 1 to 99 days) in the OXN PR group and 68.0 days (range: 2 to 103 days) in the placebo group. The protocol-planned duration of treatment in the Double-blind Phase was 84 days (12 weeks); 104 subjects (69.3%) in the OXN PR group and 76 subjects (49.4%) in the placebo group received study medication for at least 84 days.

A total of 126 subjects (84.0%) in the OXN PR group and 106 subjects (68.8%) in the placebo group reported AEs. This is not unexpected in a study of an active opioid treatment and inactive placebo, and is consistent with observations from studies of dopaminergic agents versus placebo in RLS. The vast majority of AEs (~95% in each treatment group) were mild or moderate in nature. There were no notable differences in the incidence of AEs for any of the sub-groups examined (> 65 years, ≤ 65 years, female, male; type of prior RLS therapy) compared to the overall Double-blind Safety population. Nausea, dry mouth, fatigue, dizziness, constipation and hyperhidrosis were reported more frequently in the OXN PR group than the placebo group. All of these events are consistent with the expected safety profile of opioid analgesics.

Treatment-related AEs (i.e. AEs that were unlikely, possibly, probably or definitely related to study medication based on Investigator assessment) were reported for 109 subjects (72.7%) in the OXN PR group and 66 subjects (42.9%) in the placebo group. A total of 365 out of 542 AEs (67.3%) in the OXN PR group and 170 out of 283 AEs (60.1%) in the placebo group were considered to be treatment-related. The most frequently occurring treatment-related AEs (reported by ≥ 5% of subjects in either treatment group) reflected the most common AEs overall, and included nausea, constipation, dry mouth, headache, somnolence, dizziness, fatigue, hyperhidrosis and pruritis.

Adverse events of special interest included opioid withdrawal syndrome and GI AEs. One subject in the OXN PR group experienced drug withdrawal syndrome during the Down-titration Period, which resolved after 9 days. Most GI AEs were mild or moderate in severity and few subjects (eight in the OXN PR group and five in the placebo group) prematurely discontinued due to GI AEs; overall GI AEs were reported by 63 subjects (42.0%) in the OXN PR group and 28 subjects (18.2%) in the placebo group. There was a very low incidence of abdominal pain and diarrhoea in the OXN PR group. Constipation was reported by 32 subjects (21.3%) in the OXN PR group and seven subjects (4.5%) in the placebo group, however the majority of constipation AEs in the OXN PR group were mild or moderate in nature and few required intervention (discontinuation/dose interruption: one subject, dose reduction: one subject; additional therapy: ten subjects). Overall only 11 subjects (7.3%) in the OXN PR group were considered to have clinically relevant constipation.

One subject (109625, OXN PR group) died during the study; the death occurred 25 days after the subject's last dose of study medication and was not considered to be related to study medication by the Investigator or Sponsor. This subject also experienced SAEs of pancreatitis (not related), pleural effusion and duodenal ulcer (unlikely related) and vomiting (possibly related). Seven other subjects in the OXN PR group experienced 11 SAEs; four SAEs were treatment-related (constipation [probably related], flank pain [possibly related], metastases to liver [unlikely related] and cholelithiasis [unlikely related]). Two subjects in the placebo group experienced SAEs (arthropod sting and wrist fracture, both not related to study medication).

Twenty-two subjects (14.7%) discontinued due to AEs in the OXN PR group compared with 10 subjects (6.5%) in the placebo group; of these 19 subjects (86.4%) in the OXN PR group and seven subjects (10.0%) in the placebo group discontinued due to treatment-related AEs.

Analyses of haematology, blood chemistry and urinalysis parameters did not reveal any clinically notable changes over the course of the study in either treatment group. Out of range values were observed for some laboratory parameters, but no trend of shifts in one particular direction was identified for any parameter in either treatment group. A similar number of abnormal values and AEs related to laboratory safety tests were reported in each treatment group, suggesting no effect of OXN PR on laboratory safety parameters.

There were no clinically notable changes in mean vital signs values over the course of the study in either treatment group. Nine subjects in the OXN PR group and six subjects in the placebo group had AEs concerning vital sign abnormalities (hypertension or hypotension); the majority were unrelated to study mediation, four were unlikely related and one was possibly related to study medication, and all were mild or moderate in severity. Based on the vital sign data available in this study, there were no vital sign abnormalities that constituted a safety signal. Few subjects had abnormal ECG findings and only three subjects had a clinically significant change from baseline in their ECG (i.e. an ECG abnormality post-baseline that was not present at baseline). These were incomplete right bundle branch block in the OXN PR group and possible infarct (maybe old) q-wave >40 ms in V1 and V2 and hypertrophy because of hypertension in the placebo group.

Conclusions: The primary efficacy analysis demonstrated superior efficacy of OXN PR versus placebo in the improvement of RLS symptom severity as measured by the IRLS scale, with a statistically significant and clinically relevant treatment difference for the IRLS sum score at Visit 9 (Week 12) of 8.15 (95% CIs: 5.46, 10.85, $p<0.001$). Notably, the significant effect of OXN PR on RLS symptoms with a clinically relevant difference of over 8 points for the IRLS sum score has not been shown overall to such an extent in dopamine agonist trials. A statistically significant treatment difference of a similar magnitude (approximately 8), with a lower 95% CI above 4, was also shown at Visits 5, 6, 7 and 8 (Weeks 2, 3, 4 and 8), and a clear effect of OXN PR on RLS symptoms was observed as early as 1 week after the start of treatment. The primary analysis results were confirmed by the results of the robustness analyses. In addition, the remitter rate and the number of subjects with at least a 50% improvement in the IRLS sum score was statistically significantly higher in the OXN PR group compared with the placebo group.

The conclusion of superior efficacy of OXN PR versus placebo in the improvement of RLS symptoms was supported by the results of the exploratory analyses on the secondary efficacy endpoints.

Subjects were regularly and thoroughly evaluated for potential augmentation throughout the study and there were no confirmed cases of augmentation in either treatment group, despite a distinctive and detailed augmentation analysis during the trial.

As expected for a study of an opioid analgesic compared with inactive placebo, the incidence of AEs was higher in the OXN PR group than the placebo group. The most frequently reported treatment-related AEs in the OXN PR group were consistent with the known safety profile of the opioid analgesic class of drugs. The majority of AEs (~95% in each treatment group) were of mild or moderate severity. Overall, there were no new or unexpected observations relating to safety in this population of subjects with RLS.

These results show that OXN PR is an effective and relatively safe treatment in idiopathic RLS.

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