2. SYNOPSIS

<table>
<tr><td>Name of Company:
Napp Pharmaceuticals Limited</td><td>INDIVIDUAL STUDY TABLE</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Name of Finished Product:
Oxycodone / naloxone prolonged release tablets (OXN PR)</td><td rowspan="2">Referring to Part … of the Dossier

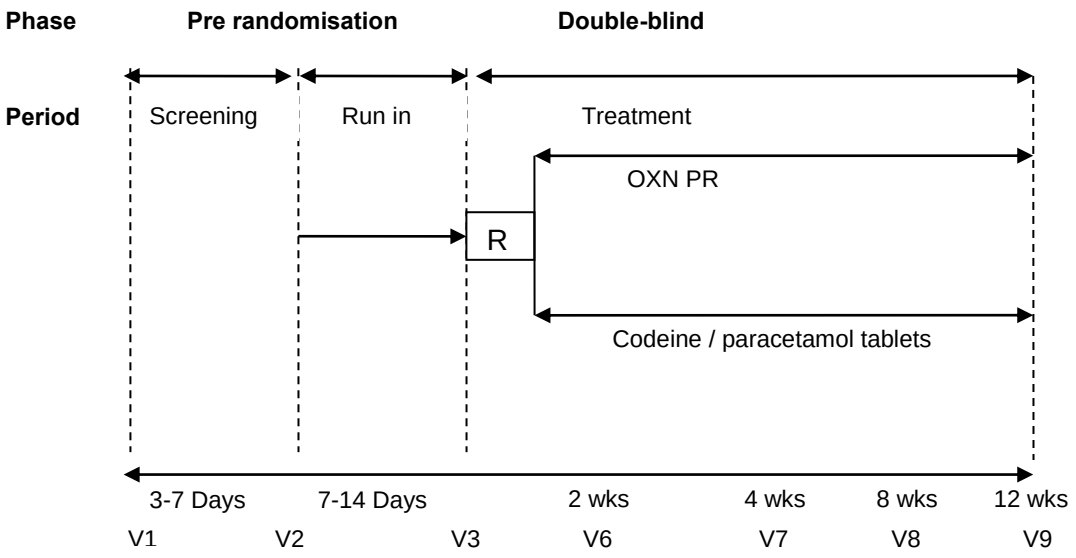
Volume: Page:</td></tr>
<tr><td>Name of Active Ingredient:
Oxycodone hydrochloride / naloxone hydrochloride</td></tr>
<tr><td colspan="3">Title of the Study: A double-blind, double-dummy, parallel group, randomised study to compare the efficacy and tolerability of oxycodone/naloxone prolonged release (OXN PR) and codeine/paracetamol in the treatment of moderate to severe chronic low back pain or pain due to osteoarthritis.</td></tr>
<tr><td colspan="3">Investigators: A total of 36 centres in the UK enrolled subjects. A further five sites were given ethics approval and received study medication supplies, but did not enrol any subjects.</td></tr>
<tr><td colspan="3">Publication (Reference): None</td></tr>
<tr><td>Study Dates:
6 Feb 2009 to 24 Mar 2010</td><td>Study Status:
Completed</td><td>Phase of Development:
Phase 4</td></tr>
<tr><td colspan="3">Objectives: The primary objective of the study was to show non-inferiority of oxycodone/naloxone prolonged release combination tablets (OXN PR) compared to codeine/paracetamol tablets in the management of moderate to severe pain as assessed by average daily pain scores (BS-11 pain scores).
Exploratory objectives were:
To compare the Western Ontario and McMaster Universities Osteoarthritis Composite Index (WOMAC) composite scores and stiffness subscale scores between OXN PR and codeine/paracetamol tablets in those subjects with osteoarthritis (OA)
To assess the severity and interference of pain based on the Brief Pain Inventory, short form (BPI-SF) (Cleeland and Ryan, 1994)
To compare the frequency of rescue medication use for breakthrough pain between OXN PR and codeine/paracetamol tablets
To compare the quality of sleep using the Medical Outcomes Survey (MOS) sleep scale
To compare opioid induced constipation in the OXN PR and codeine/paracetamol treated subjects as measured by the Bowel Function Index (BFI)
Subject assessment of opioid induced constipation, constipation symptom severity, impact and bothersomeness based on the Patient Assessment of Constipation Symptoms (b) (PAC-SYM[b])
To assess the frequency of laxative medication use and number of bowel movements
To assess the impact of pain and constipation on subjects' quality of life using the EQ-5D VAS scale and the impact of constipation on subjects' quality of life using the PAC-SYM(b) bothersomeness questions.</td></tr>
<tr><td colspan="3">Methodology: This was a randomised, double-blind, double-dummy, parallel group, 12-week study to assess the efficacy and tolerability of OXN PR compared to codeine/paracetamol tablets in the treatment of moderate to severe chronic low back pain or moderate to severe pain due to OA of the hip and /or knee.
The study comprised a screening period of 3 to 7 days duration (this was changed to 1 to 14 days duration by Protocol Amendment 1, 3 March 2009), a run-in period of 7 to 14 days duration, a 12-week treatment period and a follow-up telephone call 7 days after discontinuation/completion of the study.
At Visit 1, after written informed consent was obtained, the subject underwent screening for study eligibility. Subjects had a blood sample taken for routine safety analysis and an electrocardiogram (ECG) was performed. The results of these tests had to be reviewed by the Investigator as not clinically significant before the subject could proceed with the run-in period.</td></tr>
</table>

Visit 2 took place at the start of the run-in period. During the run-in period subjects continued to take their pre-study pain medication. All subjects were asked to discontinue any laxative medication they were taking and take the study laxative (bisacodyl) only if required for the duration of the run-in period.

Visit 3 occured at the end of the run-in period (7 to 14 days after Visit 2). To qualify for entry into the treatment period of the study, subjects had to have uncontrolled pain as shown by average daily pain scores of ≥ 5 on 4 of the last 7 days of the run-in period. Eligible subjects were randomised to receive OXN PR or codeine/paracetamol tablets for up to 12 weeks. During the treatment period there were two telephone calls (Visit 4 [Day 3] and Visit 5 [Day 7]) and four clinic visits (Visits 6, 7, 8 and 9 after 2, 4, 8 and 12 weeks of treatment, respectively). A visit window of ±1 day for Visits 4 to 9 was added by Protocol Amendment 2 (12 June 2009). Unscheduled visits for dose titration of study medication were allowed in between the scheduled assessment visits.

End-of-study procedures were completed at Visit 9 or at discontinuation. A follow up telephone call was made to the subject 7 days after discontinuation/completion of the study to obtain adverse event (AE) data. A visit window of +3 days for the follow up telephone call was added by Protocol Amendment 2 (12 June 2009).

Study Design Graphic:



R = randomisation to study treatment
Note: V4 and V5 are telephone visits 3 days and 7 days after V3

Number of Subjects: It was planned to randomise a total of 244 subjects to treatment with the aim that 196 subjects (98 subjects in each treatment group) would complete the study. A total of 297 subjects entered the run-in period, 250 subjects were randomised (124 subjects received OXN PR, 123 received codeine/paracetamol and three did not receive any study medication) and 135 subjects completed the study.

All 247 subjects who received study medication were included in the double-blind safety population, 245 subjects (OXN PR: 123, codeine/paracetamol: 122) were included in the intention-to-treat (ITT) population, and 148 subjects (OXN PR: 68, codeine/paracetamol: 80) were included in the per protocol (PP) population. The main reason for exclusion from the PP population was duration of treatment <56 days, which resulted in exclusion of 95 subjects.

Indication and Criteria for Inclusion: Male or female subjects aged 18 years or older with; (a) a clinical diagnosis of degenerative or primary OA whose primary pain site was the hip(s) and/or knee(s) and that required around-the-clock opioid therapy or (b) moderate to severe chronic low back pain e.g. OA, spinal stenosis, spondylolisthesis, failed back surgery, scoliosis, or discogenic disorders such as herniated disc. At study entry subjects had to be taking codeine/paracetamol combination tablets up to a maximum dose of 120 mg per day of codeine or tramadol up to a maximum daily dose of 100 mg or dihydrocodeine/paracetamol tablets up to a maximum dose of 120 mg dihydrocodeine per day. Subjects with secondary OA (e.g. fracture, septic, agromegaly) or rheumatoid arthritis were excluded from the study.

For entry into the double-blind treatment period, subjects had to have uncontrolled pain as shown by average daily pain scores of ≥ 5 on 4 of the last 7 days of the run-in period, and had to have shown compliance with completing daily diaries and use of bisacodyl laxative medication during the run-in period.

Duration of Treatment:

Pre-randomisation phase: 3 to 7 day screening period (this was changed to a 1 to 14 day screening period by Protocol Amendment 1, 3 March 2009), followed by a 7 to 14 day run-in period.

Treatment period: up to 12 weeks treatment with OXN PR or codeine/paracetamol tablets.

Treatment Schedule: Eligible subjects were randomised to either OXN PR or codeine/paracetamol tablets and started treatment on the lowest dose of study medication (OXN PR 5/2.5 q12h or codeine/paracetamol 15/500 (2 tablets q6h). Subjects received double-blind study medication for up to 12 weeks. Titration of the study medication was allowed at any time during the treatment phase if subjects had uncontrolled pain. Titration of OXN PR to a dose of 10/5 q12h and if necessary further titration to a dose of OXN PR 20/10 q12h was permitted. Titration of codeine/paracetamol to a dose of 30/500 (2 tablets, q6h) was permitted. If a subject did not have sufficient pain control (as assessed by the subject and Investigator) on the highest dose of study medication and use of rescue medication they were withdrawn from the study.

Test Treatment, Dose, and Mode of Administration:

Treatment Phase

Study Medication	Dosage Form	Unit Strength	Dosing Frequency	Mode of Administration	Batch numbers
Prolonged-release oxycodone/ naloxone (OXN PR)	Tablets	5/2.5, 10/5 and 20/10 mg oxycodone/ naloxone combination	q12h	Oral	PN3331 (5/2.5) PN3351 (10/5) PN3343 (20/10)
Matched placebo for codeine/ paracetamol	Tablets	Matching placebos for 15/500 and 30/500 mg	2 tablets q6h	Oral	PN3371 PN3372 PN3373

All subjects started treatment with OXN PR 5/2.5 every 12 hours (q12h). Dose titration to a dose of OXN PR 10/5 q12h and subsequently OXN PR 20/10 q12h was allowed if the subject had uncontrolled pain, as assessed by the Investigator and subject.

Reference Treatment, Dose, and Mode of Administration:

Treatment Phase

Study Medication	Dosage Form	Unit Strength	Dosing Frequency	Mode of Administration	Batch numbers
Codeine/ paracetamol	Tablets	15/500 and 30/500 mg codeine/paracetamol tablets	2 tablets q6h	Oral	PN3356 (15/500) PN3357 (30/500)
Matched placebo for OXN PR	Tablets	Matched placebos for OXN PR 5/2.5,10/5 and 20/10 mg	q12h	Oral	PN3226 (5/2.5) PN3228 (10/5) PN3229 (20/10)

All subjects started treatment with codeine/paracetamol tablets 15/500 mg, 2 tablets every 6 hours (q6h). Dose titration to a dose of codeine/paracetamol 30/500 mg, 2 tablets q6h was allowed if the subject had uncontrolled pain, as assessed by the Investigator and subject.

Concomitant Medication Including Rescue:

Pain

Rescue Medication	Dosage Form	Unit Strength	Dosing Frequency	Mode of Administration	Batch number
Ibuprofen	Tablets	400 mg	As required (PRN) up to 3 times a day	Oral	PN3362

During the treatment period ibuprofen tablets 400 mg could be used by the subject to treat breakthrough pain, up to a frequency of 3 times per day (approximately 6 hourly).

Laxative

Rescue Medication	Dosage Form	Unit Strength	Dosing Frequency	Mode of Administration	Batch number
Bisacodyl	Tablets	5 mg	q3d PRN 2 tablets	Oral	PN3361

q3d=every 3 days

- All laxative products, with the exception of laxative rescue and fibre supplementations or bulking agents, were prohibited during the run-in and treatment periods. Subjects taking daily fibre supplementation or bulking agents were eligible if they could be maintained on a stable dose and regimen throughout the study, and in the Investigator's opinion were willing and able to maintain adequate hydration.
- At the discretion of the Investigator, the bisacodyl dose could have been lowered (to 5 mg) if the Investigator/subject felt that the dose was higher than what was required to provide an adequate bowel movement. If the dose was lowered to 5 mg the lowered dose was counted as a full single dose for this subject.
- Laxative regimen: as rescue medication for constipation, bisacodyl could be used no sooner than 72 hours after a subject's most recent bowel movement (BM). If there was no BM within 24 hours following bisacodyl use, bisacodyl use could have been repeated. If there was still no BM within 24 hours following the second use of bisacodyl, an enema could have been used. If there was still no BM following the use of the enema, the subject was discontinued from the study. There was a limit of 5 intakes of laxative per week.
- Anti-diarrhoeals could be used during the study if they were considered necessary by the Investigator.
- Concomitant medications that may have affected bowel function were only used if absolutely necessary.

Anti-emetic medications

- If subjects required treatment for nausea or vomiting, an anti-emetic was prescribed at the Investigator's discretion.

Proton Pump Inhibitor (PPI)

Rescue Medication	Dosage Form	Unit Strength	Dosing Frequency	Mode of Administration	Batch number
Omeprazole	Tablets	20 mg	PRN, up to once a day	Oral	PN3363

Subjects were advised to take an omeprazole 20 mg tablet once in the evening on any day that they took ibuprofen as rescue medication. If a subject was already taking a different PPI before study entry they could continue to take this medication during the study at the recommended dose instead of using omeprazole.

Criteria for Evaluation:

Analysis Populations:

Intent-to-treat (ITT) population: all subjects who received study medication and who participated in at least one post-baseline assessment.

Per-protocol (PP) population: all subjects who did not substantially deviate from the protocol.

Pre-randomisation safety population: all subjects who participated in the run-in period.

Double-blind safety population: all subjects who were randomised and had at least one safety assessment.

Efficacy Assessments:

Primary efficacy variable:

- Average daily pain score (BS-11) recorded each day in the diary.

Exploratory efficacy variables:

- Subject assessment of pain and locomotor function using the WOMAC VA3.1.

- BPI-SF (Cleeland and Ryan, 1994). Subjects scored four items regarding pain severity on a scale of 0 to 10 (0=no pain, 10=pain as bad as you can imagine), seven items regarding pain interference with daily activities on a scale of 0 to 10 (0=does not interfere, 10=completely interferes) and one item regarding pain relief as a percentage (0%=no relief, 100%=complete relief).
- Pain rescue medication use.
- MOS Sleep scale.
- BFI assessed for the last 7 days. The BFI was the mean of the following items (assessed at each visit by the subject to the clinic and also by telephone at Visit 5): Ease of defecation (numerical analogue scale [NAS], 0=easy/no difficulty; 100=severe difficulty), Feeling of incomplete bowel evacuation (NAS, 0=not at all, 100=very strong), Personal judgment of constipation (NAS, 0=not at all, 100=very strong).
- PAC-SYM(b); this is an adaptation of the PAC-SYM (Frank *et al*. 1999), which includes the first 12 questions of the validated PAC-SYM and an additional measure of bothersomeness of the symptoms of constipation. For each symptom, the subject is asked to grade both the severity of the symptom and the degree of bothersomeness of the symptom. Severity is rated on a 5-point scale, where 0=absent and 4=very severe. Bothersomeness is rated on a 5-point scale, where 0=not at all and 4=extremely. There is one additional question at the end, assessing the frequency of bowel movements in the past 7 days. Each subject was asked if he/she had fewer bowel movements than they would have liked over the past 7 days, where 0=none of the time and 4=all of the time. They were then asked how bothered they were about the frequency, where 0=not at all and 4=extremely.
- Frequency of laxative use and number of bowel movements (recorded for the last 7 days).
- EQ-5D. Subjects were asked to complete the EQ-5D questionnaire and VAS three times; once to describe their health regarding their pain, once to describe their health regarding their constipation, and once to describe their health regarding their general condition.

Safety Assessments: Safety was assessed using AEs (learned through spontaneous reports), clinical laboratory results, vital signs, physical examinations, and ECGs.

Statistical Methods:

Sample Size Rationale: From a similar study (BUP4004) which utilised the average BS-11 pain score as the primary endpoint in OA pain subjects, the mean and standard deviation (SD) of the average BS-11 pain score during Weeks 11-12 was 4.2 and 2.61 for the codeine/paracetamol arm from a sample of 102 subjects.

To achieve a study with 80% power at the 1-sided 5% significance level and defining non-inferiority to be a relative difference <1.25, a sample size of 98 subjects per treatment group was required, i.e. a total of 196 subjects completing the study.

From previous studies it was estimated that there would be a drop-out rate of approximately 20% during the treatment phase, hence the study required 244 subjects to be randomised to treatment.

Additionally from previous studies it was estimated that there would be a screen failure rate of approximately 30% between the screening visit and meeting the criteria to enter the treatment phase. Hence it was planned to recruit and screen a total of 350 subjects for the study.

Efficacy Analyses

Primary Analysis

A mixed-model repeated measures (MMRM) analysis of covariance of the BS-11 score was carried out on the average score taken over the periods prior to visits at Weeks 2, 4, 8 and 12. Fixed effects were included for treatment nested within visit, baseline value average BS-11 score over 7 days prior to randomisation, and baseline dose. A random intercept for subjects was used. Observations were weighted by the number of individual days contributing to the average BS-11 score. An unstructured within-subject correlation matrix was used.

The model produced estimates for the mean BS-11 score at Week 12. The null and alternative hypotheses were:

- Null: OXN PR - 1.25 codeine/paracetamol > 0
- Alternative: OXN PR - 1.25 codeine/paracetamol < 0

The t-test for the corresponding contrast was used at the 1-sided 5% significance level. Confidence intervals (CIs) at the 90% level were displayed for the treatment differences at all the visits.

The primary analysis was performed on both the ITT and PP populations.

Exploratory Analysis

Pain rescue medication and laxative intake were recorded in daily dairies and hence were analysed in an identical manner to the primary efficacy variable.

BFI, number of bowel movements, and PAC-SYM(b) were measured at Weeks 2, 4, 8 and 12. Hence a MMRM similar to the primary efficacy analysis was used, with the difference that the observations received equal weight.

BPI-SF, WOMAC, EQ-5D, and the MOS sleep scale were only observed at the final visit (Visit 9) and at randomisation (Visit 3), hence a simple analysis of covariance (ANCOVA) was used to compare treatments adjusting for the baseline value.

No formal hypothesis testing was performed for the exploratory efficacy variables, only 95% CIs on treatment difference (by visit where appropriate) were displayed.

Laxative intake and BFI were also summarised separately for subjects in the ITT who had a BFI score ≥ 28.8 at the baseline visit (the constipated ITT population). This score represents the upper limit of a reference range of BFI values (0 to 28.8), in which 95% of chronic pain patients who are not constipated lie (Ueberall et al, 2011).

Exploratory statistical analyses were repeated on subjects in the ITT population who had severe pain (defined as a score ≥ 7 on the pain intensity scale) at the baseline visit.

Safety Analyses

The incidence of AEs was tabulated. Clinical laboratory results, vital signs and ECG findings were summarised.

Results: The study population comprised 89 male and 158 female subjects with a mean age of 64 years (range: 27 to 89 years). The majority (97.6%) were Caucasian. Based on medical history data, 69.2% of subjects had OA and 36.0% of subjects had back pain. Prior opioid medication included codeine/paracetamol for 63.2% of subjects, tramadol for 17.8% of subjects, dihydrocodeine/paracetamol for 17.0% of subjects, and dihydrocodeine for 4.9% of subjects (subjects may have taken more than one prior opioid medication). There were no notable differences between the treatment groups in subject demographic/baseline characteristics, except that the mean BFI score at baseline (Visit 3) was higher for the OXN PR group than the codeine/paracetamol group. Mean (SD) BFI scores were 29.03 (30.751) vs. 20.38 (24.334), respectively, in the ITT population and 59.49 (17.505) vs. 51.21 (14.706) in the constipated ITT population.

Sixty-three subjects (50.8%) in the OXN PR group and 49 subjects (39.8%) in the codeine/paracetamol group prematurely discontinued from the study. The reasons for discontinuation were: AEs (OXN PR: 25.8%; codeine/paracetamol: 16.3%), lack of therapeutic effect (OXN PR: 11.3%; codeine/paracetamol: 8.9%), subject's choice (OXN PR: 8.9%; codeine/paracetamol: 7.3%), administrative (OXN PR: 4.0%; codeine/paracetamol: 6.5%) and lost to follow up (OXN PR: 0.8%; codeine/paracetamol: 0.8%).

Efficacy: Note that Visit 3 occurred at baseline (end of run-in) and Visit 9 was the end of study visit (Week 12).

Primary Endpoint

BS-11 pain score

The average daily pain score (mean BS-11 pain score, ITT population) was similar for both treatment groups at Visit 3 (OXN PR: 6.79 [SD: 1.195]; codeine/paracetamol: 6.77 [SD: 1.212]) and decreased (improved) at each visit after Visit 3, with mean (SD) scores at Visit 9 of 4.20 (2.139) for the OXN PR group and 4.64 (2.046) in the codeine/paracetamol group.

The primary efficacy MMRM analysis was performed on the PP population and adjusted for baseline BS-11 score and baseline dose. Non-inferiority was defined to be a relative difference <1.25 for OXN PR – codeine/paracetamol. Non-inferiority of OXN PR to codeine/paracetamol was demonstrated as the difference of OXN PR – 1.25 x codeine/paracetamol for the average pain daily score at Visit 9 (Week 12) was less than 0 (estimate: -3.68, 90% CIs: -5.65, -1.71, p=0.002), allowing the null hypothesis to be rejected and the alternative hypothesis of non-inferiority to be accepted. The analysis was also performed on the ITT population to test the robustness of the results on the PP population. The results of the robustness analysis on the ITT population confirmed the result for the PP population (estimate of difference of OXN PR – 1.25 x codeine/paracetamol at Visit 9 [Week 12]: -2.58, 90% CIs: -3.88, -1.27, p=0.001).

The primary efficacy MMRM analysis was repeated in an exploratory manner for the sub-group of subjects with severe pain (defined as a score ≥ 7 on the pain intensity scale) at the baseline visit. The results confirmed the findings of the primary efficacy analysis on average daily pain score in both the PP population (estimate of difference of OXN PR – 1.25 x codeine/paracetamol at Visit 9 [Week 12]: -3.97, formal 90% CIs: -7.10, -0.83, formal p-value=0.039) and the ITT population (estimate of difference of OXN PR – 1.25 x codeine/paracetamol at Visit 9 [Week 12]: -2.40, formal 90% CIs: -4.51, -0.28, formal p-value=0.063).

The MMRM analysis of the BS-11 score was also carried out on the average score taken over the periods prior to visits at Weeks 2, 4, 8 and 12. The conclusions based on this average score analysis were the same as the conclusions at Visit 9 (Week 12).

Exploratory Endpoints

All exploratory endpoints were summarised and analysed for the ITT population adjusting for the baseline value. There was no significant difference between the treatment groups for any of the exploratory efficacy endpoints, with 95% CIs for the treatment difference (OXN PR – codeine/paracetamol) at Visit 9 (Week 12) including 0 for all endpoints. This was true for both the ITT population and the sub-group of the ITT population with severe pain at baseline. No formal hypothesis testing was performed for the exploratory endpoints; only 95% CIs for the treatment difference were provided. Results for the exploratory endpoints are summarised below.

Modified BPI-SF

The BPI-SF pain severity subscore (the mean of the four items that assessed the severity of the subject's pain) was very similar for both treatment groups at each visit. The mean (SD) pain severity subscore decreased (improved) from 6.20 (1.297) at Visit 3 to 4.79 (2.462) at Visit 9 in the OXN PR group, and from 6.30 (1.362) at Visit 3 to 4.80 (2.284) at Visit 9 for the codeine/paracetamol group. The treatment difference (OXN PR – codeine/paracetamol) at Visit 9 (Week 12) was not statistically significant (estimate: 0.0; 95% CIs: -0.55, 0.60 from ANCOVA).

The BPI-SF pain interference subscore (the mean of the seven items that assessed the impact of pain on daily functions) was also similar for both treatment groups at each visit. The mean (SD) pain interference subscore decreased (improved) from 5.83 (2.079) at Visit 3 to 4.52 (2.718) at Visit 9 in the OXN PR group, and from 5.92 (1.815) at Visit 3 to 4.66 (2.539) at Visit 9 for the codeine/paracetamol group. The treatment difference (OXN PR – codeine/paracetamol) at Visit 9 (Week 12) was not statistically significant (estimate: -0.1; 95% CIs: -0.67, 0.54 from ANCOVA).

Pain rescue medication use

The frequency of intakes of pain rescue medication was numerically slightly higher for the OXN PR group than the codeine/paracetamol group for each time period. Between Visit 8 and Visit 9 (a 4-week period), the mean (SD) number of intakes was 13.2 (23.31) in the OXN PR group and 9.4 (19.94) in the codeine/paracetamol group; the median number of intakes was 0 for both groups. However, the mean daily dose was similar (within 60 mg) for both treatment groups for each time period, with mean (SD) daily doses of ibuprofen of 293 mg (372.6 mg) for the OXN PR group and 288 mg (404.7 mg) for the codeine/paracetamol group between Week 8 and Week 12 (Visit 8 and Visit 9). A total of 26.6% of subjects in the OXN PR group and 39.0% of subjects in the codeine/paracetamol group took no pain rescue medication. The treatment difference (OXN PR - codeine/paracetamol) for the overall number of days with pain rescue medication intake at Visit 9 (Week 12) was not statistically significant (estimate: -1.83; 95% CIs: -5.64, 1.98 from MMRM ANCOVA).

WOMAC osteoarthritis index

There were no notable differences between the treatment groups in the WOMAC section scores for pain, stiffness or difficulty performing daily activities, or in the WOMAC overall scores, or in the scores for each of the individual questions at any visit. For both treatment groups, there was a modest decrease (improvement) in the score for each of the 24 questions between Visit 3 and Visit 9. In the full ITT population, the WOMAC overall score decreased by 14% in the OXN PR group and 16% in the codeine/paracetamol group. The treatment difference (OXN PR - codeine/paracetamol) at Visit 9 (Week 12) for the WOMAC overall score was not statistically significant (estimate: -45.2; 95% CIs: -74.55, 164.88 from ANCOVA). Similar results were obtained in the sub-group of subjects in the ITT with a diagnosis of pain due to OA (i.e. excluding subjects with a diagnosis of low back pain), the WOMAC overall score decreasing by 14% in the OXN PR group and 19% in the codeine/paracetamol group.

MOS sleep scale

The mean scores for the MOS sleep scale at Visit 9 were very similar for both treatment groups. Comparison of the treatment groups using an ANCOVA showed that there were no significant differences between the treatment groups for any of the MOS scale questions. The estimate of the treatment difference (OXN PR – codeine/paracetamol) at Visit 9 (Week 12) for the MOS total score was 0.0 (95% CIs: -0.20, 0.21).

BFI

The estimate of the treatment difference (OXN PR – codeine/paracetamol) for the BFI at Visit 9 (Week 12) was not statistically significant (estimate: 10.08, 95% CIs: -4.49, 24.65, from MMRM ANCOVA). Observations based on arithmetic mean BFI values showed that the mean BFI score decreased by 5.31 (from 29.03 [SD: 30.751] at Visit 3 to 23.72 [SD: 28.820] at Visit 9) in the OXN PR group. In contrast, the BFI score increased by 2.25 (from 20.38 [SD: 24.334] at Visit 3 to 22.63 [SD; 27.766] at Visit 9) in the codeine/paracetamol group, although neither of these observations represented a clinically relevant change from baseline. There was a decrease (improvement) in mean scores from baseline to end of study for all three items ('ease of defecation', 'feeling of incomplete bowel movement' and 'judgement of constipation') in the OXN PR group. In contrast, there was an increase in mean scores from baseline to end of study for all three items in the codeine/paracetamol group.

The BFI was also summarised for the sub-group of subjects in the ITT population with a BFI score ≥ 28.8 at baseline (the constipated ITT population). This comprised 56 subjects in the OXN PR group and 41 subjects in the codeine/paracetamol group. Observations based on arithmetic mean values showed that there was a decrease (improvement) of 22.75 in the mean BFI score for the OXN PR group (mean values of 59.49 [SD: 17.505] at Visit 3 and 36.74 [SD: 29.501] at Visit 9), which was more than the previously established minimum clinically relevant change of 12 (Rentz et al, 2009). There was a smaller decrease (improvement) of 9.38 in the mean BFI score for the codeine/paracetamol group (mean values of 51.21 [SD: 14.706] at Visit 3 and 41.83 [SD: 30.534] at Visit 9). The same trend for at least a 2-fold greater improvement in BFI scores in the OXN PR group compared with the codeine/paracetamol group for the constipated ITT population was also observed for each individual item of the BFI. This was particularly noticeable for 'judgement of constipation', for which mean scores improved by 23.85 in the OXN PR group and 6.36 in the codeine/paracetamol group. It should be noted that the BFI scores for the constipated ITT population were only descriptively summarised and were not subjected to formal statistical analysis.

PAC-SYM(b) patient assessment of constipation

The mean PAC-SYM(b) scores for symptoms, degree of bother and frequency of constipation decreased (improved) from Visit 3 to Visit 9 for the OXN PR group. The mean (SD) scores were 11.4 (10.66), 10.0 (10.84) and 2.0 (2.38), respectively at Visit 3 and 8.6 (10.11), 7.5 (10.12) and 1.7 (2.35), respectively, at Visit 9. In contrast, the mean PAC-SYM(b) scores for symptoms, degree of bother and frequency of constipation increased (worsened) from Visit 3 to Visit 9 in the codeine/paracetamol group. The mean (SD) scores were 7.5 (8.23), 6.1 (8.10) and 1.3 (1.83), respectively at Visit 3 and 8.2 (8.91), 7.2 (9.03) and 1.7 (2.30), respectively, at Visit 9. However, the treatment difference (exploratory) for the PAC-SYM(b) score at Visit 9 (Week 12) was not statistically significant (estimate: -0.15; 95% CIs: -10.2, 10.52, from MMRM ANCOVA).

Bowel movements

There was little change in the number of bowel movements in either treatment group during the study. The mean number of days that the subject had a bowel movement in the last 7 days was 5.5 (SD: 1.96) for the OXN PR group and 6.0 (SD: 1.49) for the codeine/paracetamol group at Visit 3, and 5.4 (SD: 2.11) for the OXN PR group and 5.7 (SD: 1.86) for the codeine/paracetamol group at Visit 9. The treatment difference (OXN PR - codeine/paracetamol) for the number of bowel movements at Visit 9 (Week 12) was not statistically significant (estimate: 0.93; 95% CIs: -1.36, 3.22, MMRM ANCOVA).

Laxative medication use

Laxative medication use was summarised for the period between each visit (periods of between 1 and 4 weeks). The mean number of intakes of study laxative medication was low (0.6 to 2.0 intakes) for both treatment groups over each period, with only small differences between the treatment groups (no more than 0.4) in mean values for each period. The median number of intakes of laxative medication was 0 for both treatment groups for all periods. The treatment difference (OXN PR - codeine/paracetamol) for the overall number of days with study laxative medication intake at Visit 9 (Week 12) was not statistically significant (estimate: 0.77; 95% CIs: -0.85, 2.39, MMRM ANCOVA).

Study laxative intake was also summarised for the constipated ITT population. Laxative intake was slightly higher for the constipated ITT population compared with the full ITT population in both treatment groups for all periods, with mean values ranging from 1.0 to 2.5 intakes in each period. Post-baseline (Visit 3) differences between the treatment groups remained small (up to 0.6 intakes more for the codeine/paracetamol group than the OXN PR group for each period).

Quality of life (EuroQol EQ-5D)

There was little change in the EQ-5D total score regarding constipation, pain or general condition in either treatment group from Visit 3 to Visit 9. The treatment difference (OXN PR - codeine/paracetamol) at Visit 9 (Week 12) was not statistically significant for the EQ-5D regarding general condition (estimate: 0.1; 95% CIs: -0.31, 0.46), constipation (estimate: 0.0; 95% CIs: -0.44, 0.42) or pain (estimate: 0.2; 95% CIs: -0.18, 0.56, ANCOVA).

Safety: The median duration of treatment was 56.0 days (range: 1-96 days) in the OXN PR group and 63.2 days (range: 2-97 days) in the codeine/paracetamol group. The protocol-planned duration of treatment was 84 days (12 weeks); 51 subjects (41.1%) in the OXN PR group and 66 subjects (53.7%) in the codeine/paracetamol group received study medication for at least 84 days. The most common reasons for premature discontinuation were AEs (OXN PR: 25.8%; codeine/paracetamol: 16.3%), lack of therapeutic effect (OXN PR: 11.3%; codeine/paracetamol: 8.9%) and subject's choice (OXN PR: 8.9%; codeine/paracetamol: 7.3%).

Adverse events were reported by a similar number of subjects in the OXN PR group (95 subjects [76.6%]) and the codeine/paracetamol group (100 subjects [81.3%]). The most common AEs (reported by more than 5% of subjects in either treatment group) were constipation, nausea, headache, diarrhoea, dyspepsia, lower respiratory tract infection, arthralgia, dizziness and insomnia. There were no notable differences between the treatment groups in the incidence of any AE, except headache, which was reported for 12.9% of subjects in the OXN PR group and 7.3% of subjects in the codeine/paracetamol group. The number of subjects reporting gastrointestinal (GI) AEs was similar for both treatment groups (OXN PR: 47 subjects [37.9%]; codeine/paracetamol: 49 subjects [39.8%]).

The number of subjects with treatment-related AEs (i.e. AEs considered unlikely, possibly, probably and definitely related to study medication by the Investigator) was similar for both treatment groups (OXN PR: 60.5%, codeine/paracetamol: 61.0%). Treatment-related AEs reported for more than 6% of subjects were nausea, constipation, headache, diarrhea and dyspepsia. The GI AEs were considered to be treatment-related by the Investigator for most subjects (OXN PR: 39 subjects [31.5%]; codeine/paracetamol: 46 subjects [37.4%]). There were no notable differences between the treatment groups in the incidence of any treatment-related AEs, except headache, which was reported for 12.9% of subjects in the OXN PR group and 6.5% of subjects in the codeine/paracetamol group, although the incidence of AEs was not subjected to formal statistical analysis.

The majority of AEs were mild or moderate in nature. Severe AEs were reported by 14 subjects (11.3%) in the OXN PR group and 12 subjects (9.8%) in the codeine/paracetamol group; severe AEs reported by more than 2% of subjects in either treatment group were constipation (OXN PR: 3.2%; codeine/paracetamol: 1.6%) and arthralgia (OXN PR: 2.4%; codeine/paracetamol: 0.8%).

There were no deaths during the study. Three subjects (2.4%) in the OXN PR group and four subjects (3.3%) in the codeine/paracetamol group reported SAEs as follows:

In the OXN PR group, one subject had carotid artery stenosis and one subject experienced joint effusion (both unrelated to study medication) and one subject experienced diarrhoea, rectal haemorrhage and abdominal pain that were considered possibly related to study medication by the Investigator. The Investigator changed the causality of the diarrhoea, rectal haemorrhage and abdominal pain to 'unlikely to be related' after the study, when the hospital report indicated colitis as a cause of the events.

In the codeine/paracetamol group, one subject had a head injury, one subject experienced deep vein thrombosis, one subject experienced atrial fibrillation and one subject experienced angina on two separate occasions; all these events were assessed as not related to study medication by the Investigator, except the deep vein thrombosis, which was considered possibly related to study medication by the Investigator. The atrial fibrillation (atrial flutter with left bundle branck block in the ECG at Visit 9) was not considered to be serious by the Investigator, but was considered as serious and reported as such by the Sponsor. The Sponsor assessed the atrial fibrillation as unlikely to be related to study medication. All SAEs resolved with the exception of the atrial fibrillation (ongoing) and head injury (recovered with sequalae) in the codeine/paracetamol group.

Thirty-four subjects (27.4%) discontinued due to AEs in the OXN PR group compared to 23 subjects (18.7%) in the codeine/paracetamol group. Adverse events leading to discontinuation for more than one subject in the OXN PR group were constipation (six subjects), headache (six subjects), nausea (six subjects), dizziness (four subjects), insomnia (four subjects), vomiting (three subjects), arthralgia (two subjects), diarrhoea (two subjects) and lethargy (two subjects). Adverse events leading to discontinuation for more than one subject in the codeine/paracetamol group were constipation (four subjects), nausea (three subjects), abdominal pain (two subjects), dizziness (two subjects) and insomnia (two subjects). The majority of AEs leading to discontinuation were considered to be treatment-related and all resolved within the 7-day follow up period, except three in the OXN PR group (constipation and arthralgia [two subjects]) and four in the codeine/paracetamol group (insomnia, nausea, constipation and herpes zoster). One subject in the codeine/paracetamol group who discontinued due to an AE of dizziness was lost to follow up.

There were no clinically notable changes in mean vital signs values over the course of the study in either treatment group. Analyses of haematology and biochemistry 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. The exception was gamma-glutamyl transferase in the codeine/paracetamol group, for which mean values increased from 39.7 IU/L at screening to 52.5 IU/L at end of study (although still within the normal range), with 12 subjects (10.3%) showing a shift from normal at screening to high at end of study. ECG changes were infrequent and isolated, and no ECG abnormality was directly attributable to study medication.

Conclusions: The primary efficacy analysis demonstrates that OXN PR is non-inferior to codeine/paracetamol in the management of moderate to severe pain, as assessed by average daily pain (BS-11) scores. This was confirmed in an exploratory analysis on the sub-group of subjects with severe pain at the baseline visit.

Exploratory efficacy results also suggested that OXN PR provides comparable pain relief to codeine/paracetamol, with similar improvements for both treatment groups in the BPI-SF pain severity subscore and the WOMAC section score for pain, and no statistically significant difference in pain rescue medication use.

There was only a small numerical change from baseline in mean BFI score for both treatment groups in the ITT population. The treatment difference (exploratory) was not statistically significant. In the sub-group of subjects who were constipated (BFI score ≥ 28.8) at baseline, a reduction (improvement) in arithmetic mean BFI score of 22.13 was observed for the OXN PR group. This reduction was greater than the previously established clinically relevant change in BFI score of ≥ 12, although the BFI scores in this sub-group were not subjected to formal statistical analysis. A reduction of 9.38 in the arithmetic mean BFI score was observed in the codeine/paracetamol group for the constipated ITT population. Laxative use, number of bowel movements and PAC-SYM(b) scores were similar for both treatment groups.

The general quality of life parameters (BPI-SF pain interference subscore, WOMAC section scores for stiffness and difficulty performing daily activities, MOS sleep scale and EQ-5D) provided similar results in both treatment groups. The treatment differences (exploratory) were not statistically significant.

The incidence of AEs was similar for OXN PR and codeine/paracetamol. The most frequently reported treatment-related AEs are consistent with the known safety profile of the opioid analgesic class of drugs. After the administration of OXN PR there were no additional or unexpected risks observed when compared to treatment with codeine/paracetamol.

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