1. Synopsis

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Trial Information:
Name of Sponsor/Company: Norpharma A/S, Slotsmarken 15, DK-2970 Hoersholm, Denmark Mundipharma AB, Mölndalsvägen 26, SE-412 63 Göteborg, Sweden Mundipharma AS, Vollsveien 13C, NO-1366 Lyksaker, Norway Mundipharma OY, Rajatorpantie 41B, FI-01640 Vantaa, Finland
Name of the Finished Product: Norspan®
Name of the Active Ingredient: Buprenorphine
Title of the Study: A randomised, double-blind, placebo-controlled, parallel group, multicenter study to evaluate the long-term efficacy and safety of Norspan® versus placebo Norspan in subjects with chronic, moderate to severe osteoarthritis pain in the hip and/or knee.
Principal Investigator: [redacted], Denmark
Study Centres: Nineteen centres in Denmark, Sweden, Norway and Finland
Publication: None
Phase of Development: IIIb
Design: Randomised, double-blind, placebo-controlled, parallel, multicenter study
Trial Period and Treatment Duration:
First Patient Enrolled: 25 August 2004
Last Patient Completed: 16 September 2005
Primary Objectives: • To evaluate the long-term efficacy and safety of Norspan® versus Placebo Norspan in subjects with chronic, moderate to severe, osteoarthritis pain of hip and/or knee
Secondary Objectives: • None
Methodology: The study was a randomised, double-blind, placebo-controlled, parallel group, multicenter study.
Number of Subjects: Planned: 200
Analysed: 199
Diagnose and Main Criteria for Inclusion and Trial Population: Osteoarthritis in hip and/or knee
Inclusion criteria: 1. Males and females aged more than 40 years of age. 2. Clinical diagnosis of OA of the hip and/or knee including fulfilment of the American College of Rheumatology Criteria (ACR-criteria) and grade II-IV radiographic evidence within the past year. 3. Moderate to severe pain due to OA on current therapy, as confirmed by a Western Ontario and McMaster Universities (WOMAC) OA Index. 4. Currently on scheduled dose (defined as a stable frequency and dose corresponding to at least half of the maximum daily allowed dose) of an NSAID or COX-2 inhibitor.

Exclusion criteria:
1. Subjects treated with high potent opioid analgesics for their OA pain.
2. History of chronic condition(s), in addition to OA, requiring frequent analgesic therapy.
3. Scheduled for surgery of the disease state or any other major surgery that would fall within the Screening Phase or Double-Blind Phase of the study.
4. Impaired liver function at Screening (i.e., ≥ 3 times the upper limit of normal for ASAT or ALAT).
5. Impaired kidney function at Screening (i.e., serum creatinine ≥ 177 µmol/L).

Total Expected Number of Subjects: 200 in the double-blind phase, 100 in each treatment group

Screening

The Screening Phase consisted of two visits (Screening visit and Baseline visit) approximately 1 week apart.
At the Screening visit the subject were informed of the study and study procedures, written informed consent was obtained before any study related procedures were performed. Inclusion/exclusion criteria, medical history, concomitant medication, vital signs demography and lab tests were checked. During the Screening Phase the subjects continued their NSAID or COX-2 inhbitor regimen (defined as a stable frequency and dose corresponding to at least half the maximum daily allowed dose) and discontinued all intermittent (taken as needed) opioid and/or no-opioid analgesic regimens. Paracetamol was provided as rescue analgesic for breakthrough OA pain and the subjects were asked to record daily pain by use of Pain on Movement Score (BS-11 score) and daily use of Paracetamol.

Trial Procedures

The trial phase consisted of up to 6 months treatment with visits at weekly intervals during the first two weeks and hereafter 2-weekly visits or telephone contacts (visits 6, 8, 10, 12 and 14) (13 visits in total) and a follow up contact 30 days (visit 16) after treatment discontinuation (safety follow up).
Subjects who at the Baseline visit fulfilled all in- and exclusion criteria were randomised 1:1 to either treatment with Norspan® or Placebo Norspan. Women of childbearing potential had a blood pregnancy test performed at visit 1 and 15, and a urine test performed at visit 2 and 9. At all visits the subjects were questioned about AEs and changes in concomitant medication.
All subjects were started on the lowest dose of Norspan®, 5 mg, or Placebo Norspan, and titrated up to an effective and tolerated dose or to a maximum of 20 mg while continuing their NSAID or COX-2 inhibitor regimen and taking Paracetamol as rescue medication. The first dose was given while the subject was at the investigational site and up titration to the next strength could only be done after a minimum of 3 days treatment of any given dose of Norspan®/Placebo Norspan. Down titration, as dictated by the subject tolerability, was allowed. The subjects were advised not to exceed daily intake of Paracetamol above the manufactorer's recommended dose (4000 mg/day).
Throughout the active treatment phase the subjects were asked to score and record daily pain and use of Paracetamol. At baseline and visit 2, 3, 4, 5, 7, 9, 11, 13, 15 and 16 (final visit) the subjects filled in the WOMAC OA Index, EuroQoL EQ-5D and Sleep questionnaires. At the final visit the Patient's Global Impression of Change (PGIC) questionnaire were filled in and the Investigator answered the Abuse/Diversion Questions.
The follow up visit was done as a telephone interview provided all study medication had been returned.

Test Product (IP), Dose and Mode of administration, Batch Number:

Product: Norspan®

Dose: 5, 10 and 20 mg

Administration: 7-day Buprenorphine TransDermal System

Batch Numbers:
5 mg: PN2819, PN2926
10 mg: PN2817, PN2927
20 mg: PN2815, PN2928

Duration of Treatment: 7 day screening period followed by up to 6 months double-blind treatment

Reference Therapy, Dose and Mode of Administration, Batch Number

Product: Placebo Norspan

Dose: 5, 10 and 20 mg

Administration: placebo TransDermal System

Batch Numbers:
5 mg: PN2844, PN2929
10 mg: PN2845, PN2930
20 mg: PN2846, PN2931

Criteria for Evaluation:

Efficacy Variables:	Primary efficacy variables: 1. Change in WOMAC OA Index score for pain from baseline to the end of the double-blind period (up to 6 months) Secondary efficacy variables: 1. Change in WOMAC OA Index score for stiffness, functional ability and total score between baseline and end of double-blind period 2. Average BS-11 score for pain on movement 3. Average daily rescue medication use 4. Sleep disturbance and quality 5. Patient's Global Impression of Change (PGIC) 6. Treatment duration Exploratory Efficay Variables: 1. EuroQoL EQ-5D
Safety Variables:	Adverse events, vital signs and physical examination

Statistical Considerations and Methods:

Generally all subjects were assumed statistically independent. The sample size was based on the primary endpoint, the change from baseline in the pain subscale of the WOMAC OA Index to the end of the 6 months assessment period; with 160 subjects (80 in each treatment group) the study would have 80% power at the 5% significance level to detect a difference of 1.0 between treatment groups. Assuming a ~ 10% drop out rate after randomisation approximately 200 subjects would have to be recruited (approximately 100 in each treatment group). All statistical tests were carried out as 2-sided under a 5% level of error of type I.

Primary endpoint:

The primary endpoint was analysed using analysis of covariance (ANCOVA) with treatment as a factor, and site of OA pain, season in which the subject entered the study and WOMAC OA Index (5 box score version) score for pain recorded at Baseline as covariates.

Secondary endpoints:

The secondary endpoints WOMAC OA index (5 box score version) for functional ability, WOMAC OA index for stiffness, Total WOMAC OA Index, average BS-11 score and average daily rescue medicine were analyzed and summarized as the primary endpoint.

Sleep disturbance, PGIC were analyzed using Wilcoxon two-sample test stratified by site of pain.

Quality of sleep was analyzed using proportional odds model for ordinal data.

Exploratory endpoints:

EuroQol EQ-5D consists of five questions each with a 3 item ordinal response and a VAS for self-reporting of the patient's health state today.

Responses for each of the questions were summarized as frequencies and relative frequencies for the items on the scale for visit 2 and final visit for each treatment group within each site of pain.

The VAS score was summarized by number of subjects, mean and standard deviation for visit 2 and final visit as well as mean difference and standard deviation, stratified by site of pain and treatment group.

Safety endpoints:

No formal testing of safety variables were performed.

Summary Conclusions:

Efficacy Result:

Primary endpoint:

The result of the ITT as well as PP analysis did not reach nominal statistical significance (P = 0.06)

Secondary endpoints:

The endpoints related to pain, BS-11, and the endpoint related to overall status, PGIC, both gave significant results for Norspan® compared to Placebo Norspan. For BS-11 the mean difference was -0.5 with a 95%

confidence interval of (-0.95, -0.05), P=0.03, and for PGIC the mean was 2.9 for Norspan® and 3.4 for Placebo Norspan, with P=0.02.

No differences were found for Average Daily Rescue Medication, sleep disturbance, quality of sleep and duration of treatment between Norspan® and Placebo Norspan.

Exploratory endpoints:

No obvious differences were observed.

Safety Result:

No formal testing of AEs was planned. 92 subjects (92.0%) in the Norspan® group experienced a total of 589 AEs, the figures for the Placebo Norspan group were 73 subjects (73.7%), who experienced 258 AEs. The main difference was found for Gastrointestinal Disorders, 162 versus 38 events, General Disorder and Administration Site Conditions, 177 versus 69 events, and Nervous System Disorders, 97 versus 33 events, respectively respectively. More AEs were graded as severe in the Norspan® group than in the Placebo Norspan group, 45 versus 17 in the two groups respectively.

Ten (10) SAEs were reported, 6 on Norspan® and 3 on Placebo Norspan. One SAE was reported during the run-in period. Two SAEs, both on Norspan® were evaluated by the investigators to be probably and possibly related respectively, both SAEs were moderate to severe and the subjects recovered completely.

31 subjects in the Norspan® group withdrew because of AE, whereas the number in the Placebo Norspan group was 2.

No differences were observed in vital signs (pulse and systolic and diastolic blood pressure).

Conclusion:

Patients treated more than 2 weeks and up to the 6 months were included in the IIT and PP analysis.

The result of the study did not reach statistical significance on the primary endpoint pain (p=0.06).

The effect of WOMAC pain score at baseline was strongly significant, indicating significant placebo effect.

There was a strong significant, but unexplained impact of centre and baseline values for most of the endpoints analysed, whereas no impact of season was observed

Among the secondary endpoints statistically significant differences in favour of Norspan® was seen for BS-11 pain score and Patients Global Impression of Change.

For the remaining secondary endpoints not related to WOMAC OA Index (5 box score version) score no statistically significant differences were seen. Non-compliance was an important issue in the Paracetamol reporting

Even though a formal testing of safety variables was not carried out more safety issues occurred in the Norspan® leading to a higher drop out rate. More AEs were assessed as severe in the Norspan® group, and many of the AEs seem to be related to the active ingredient, buprenorphine. Application site reactions were observed more often in the active group. Women tolerated the treatment better than men, and younger women ≤ age of 63 years tolerated the treatment better than women > 63 years of age.

The sample size and the efficacy analysis were changed during the study, due to difficulties in the recruitment the planned number of patients. Instead of using data collected after minimum 2 months treatment, data from subjects treated more than two weeks were used.

Date of Report:

05 September 2007