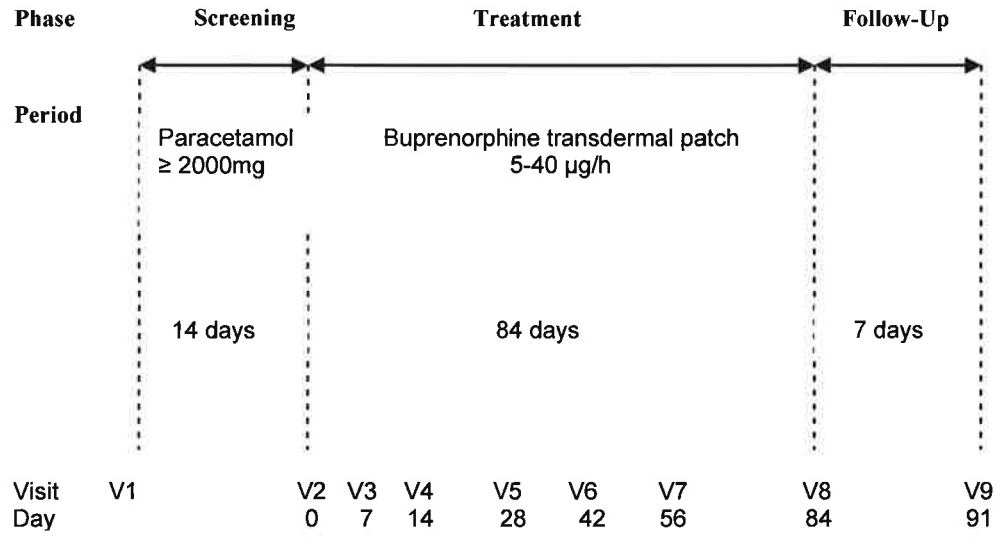
1 CLINICAL REPORT SYNOPSIS

Name of Company: Mundipharma AB		
Name of Finished Product: Norspan		**Name of Active Ingredient:** **Buprenorphine**
Protocol No.: **BUP4504**	**Temporary (T) No.:**	**EudraCT No.:** 2010-020748-37
Short Title of the Study: Norspan® efficacy and safety among elderly subjects		
Full Title of the Study: An open label, multi-centre, prospective age-group-controlled study to evaluate efficacy and safety of buprenorphine transdermal patches in subjects with chronic, moderate to severe osteoarthritis pain of the hip and/or knee.		
Investigator(s)/Site(s): 6		
Study Initiation: Planned Q42010	**Phase of Development:** Phase IV	
Objectives: The primary objective in this non-inferiority study was to evaluate the efficacy (pain intensity, BS-11) of buprenorphine transdermal patches in subjects in two different age groups: 50-60 years and ≥ 75 years with chronic, moderate to severe osteoarthritis pain.		
Study Design (Methodology): This was an open label, multi-centre, prospective age-controlled study to evaluate efficacy and safety among subjects in two different age groups treated with buprenorphine transdermal patches. Enrolled subjects were currently receiving sub-optimal non-opioid analgesic. Each subject started with a Screening Phase 14 days. At the Screening Visit the previous analgesic therapy was stopped and paracetamol treatment was started. Each subject was asked to take a maximum tolerated dose of paracetamol during the Screening Phase (≥ 2000mg but ≤ 4000mg daily). On the Baseline visit, the pain was evaluated. If it was ≥ 4 on average during the last seven days of the Screening Phase, the subject could be started on a buprenorphine transdermal patch 5µg/h treatment with the possibility to be up-titrated to a maximum of 40µg/h during the study period of 84 days.		
Study Design Graphic: 		

Number of Subjects: 39 per protocol subjects were needed per age group, in total 78 subjects. Based on experience on withdrawal in previous studies 51 subjects per age group needed to be recruited and started on a buprenorphine transdermal treatment, in total 102 subjects.

Indication and Criteria for Inclusion/Exclusion:

Indication and Criteria for Inclusion:

1. Males and females aged 50-60 or ≥ 75 years.
2. Subjects with clinical diagnosis of osteoarthritis in knee and/or hip including fulfilment of ACR-criteria and radiographic evidence not older than one year.
3. Subjects with a moderate to severe pain, confirmed by a BS-11 score ≥ 4 for their pain on average during the last seven days of the Screening Phase in their primary OA-site at the Baseline Visit.
4. Subjects should be willing to stop their current OA pain treatment and replace it with sponsor provided paracetamol with maximum tolerated daily dose intake during the Screening Phase (≥ 2000mg but ≤ 4000mg daily).
5. Female subjects of childbearing potential (including female subjects less than one year post-menopausal) must have a negative urine pregnancy test recorded prior to the first dose of study medication, be non-lactating, and willing to use adequate and highly effective method of contraception throughout the study. A highly effective method of birth control was defined as those which result in a low failure rate (i.e less than 1% per year) when used consistently and correctly such as combined oral contraceptives, sterilization, implants, injectables, some IUDs (Intrauterine Device), or vasectomised partner.
6. Subjects must read and comprehend national language (Swedish) and willing to sign informed consent.

Indication and Criteria for Exclusion:

1. Subjects recording < 4 on average during the Screening Phase on the BS-11 scale.
2. Subjects treated with high-potent opioid analgesics (e.g. morphine, fentanyl, oxycodone, methadone, hydromorphone, ketobemidone, buprenorphine) for their osteoarthritis pain.
3. Subjects treated with a regular dose for > 1 week of tramadol, codeine or dextropropoxiphene within 1 month before screening visit.
4. Subjects who require NSAID treatment (except aspirin for cardiovascular indications) or cox-2-inhibitors during the study period.
5. Subjects with history of, or ongoing, chronic condition(s), in addition to osteoarthritis, requiring frequent analgesic therapy (e.g. frequent headaches, frequent migraine, gout, rheumatoid arthritis).
6. Subjects scheduled for surgery that would fall within the study period.
7. Subjects who abused substance or alcohol, or subjects who, in the opinion of the Investigator, have demonstrated addictive or substance abuse behaviours.
8. Subjects with cancer (except basal cell carcinoma) or history of cancer in the last 5 years (except treated basal cell carcinoma).
9. Untreated depression or other psychiatric disorder in such way that participation in the study may, in the opinion of the Investigator, pose an unacceptable risk to the subject.
10. Subjects who were taking hypnotics, anxiolytics or other central nervous system depressants that, in the Investigator's opinion, may pose a risk of additional CNS depression with study medication.
11. Subjects who were taking adjuvant analgesics such as antidepressants and anti-convulsants.
12. Dermatological disorder or non-intact skin at any relevant patch application site that precludes proper placement and/or rotation of patch placement.
13. Subjects who received an intra-articular steroid injection within 6 weeks prior Screening Visit or subjects who required steroid treatment (oral, intra-muscular, intra-venous, intra-articular, epidural or other corticosteroid injections) during the study period.
14. Subjects with joint evacuation 6 weeks prior Screening Visit and during the study.
15. Subjects who were taking monoamine oxidase inhibitors (MAOI's) or have taken MAOI's within 2 weeks before Screening Visit.

16. Participated in a clinical research study involving a new chemical entity within 30 days before Screening Visit.
17. Subjects with known tolerance and/or lack of effect of buprenorphine.
18. Subjects with known allergy, hypersensitivity or other contraindications to opioids, transdermal delivery systems or patch adhesives.
19. Ongoing requirement for and treatment with direct external heat sources such as heat lamps, electric blankets, saunas, heating pads and heated waterbeds.
20. Subjects with new physiotherapy regimen scheduled to commence during Screening Phase or Treatment Phase of the study.
21. Subjects who could not or would not cut the hair at the patch site for proper placement of the patch.
22. Any other contraindications listed in the Summary of Product Characteristics for Norspan.
23. Subjects who were unsuitable for any other reason to receive study medication in the opinion of the Investigator.

Reference Treatment, Dose, and Mode of Administration:

No reference treatment

Concomitant Medication Including Rescue:

The following concomitant medications were permitted:

1. Aspirin for cardiovascular indications up to a maximum daily dose of 320 mg.
2. Study provided paracetamol could be used as rescue medication throughout the study.
3. Any use of glucoseamine should be stable from the Screening Visit until the Completion/Discontinuation Visit.
4. Any physiotherapy regimen should be stable from the Screening Visit until the Completion/Discontinuation Visit.

The following concomitant medications or therapies were not permitted during the study:

1. Any opioid formulations (low and/or high potent) other than study drug were prohibited throughout the course of the study.
2. Non-opioid analgesics (e.g. NSAID's and/or aspirin except aspirin for cardiovascular indications) or coxiber should be discontinued at the Screening Visit until Completion/Discontinuation Visit.
3. New analgesic therapy (such as local anaesthetic injections, joint evacuation).
4. No intra-articular hyaluron acid injection had to be given 6 months prior to Screening visit and during the study.
5. Any joint evacuation was not to be carried out before 6 weeks prior to Screening Visit and during the study.
6. Steroids (intra-articular) in the 6 weeks prior to Screening Visit or during the study. Subjects requiring steroid treatment (oral, intra-muscular, intra-venous, intra-articular, epidural or other corticosteroid injections) were removed from the study.
7. Adjuvant analgesics such as anti-convulsants (e.g. gabapentin, pregabalin).
8. TENS received prior to study entry had to be discontinued at the Screening Visit.
9. It was not allowed to relieve the subjects pain by any other treatment or intervention.

Duration of Treatment and Study Duration: 2 week Screening Phase followed by a 12-week open Treatment Phase. The study ended by 1 week Follow-up Phase.

Treatment Schedule (Procedure):

Screening Phase (2 weeks): At the Screening visit (Visit 1) the subject discontinued its current analgesic treatment and replaced it with sponsor provided paracetamol of maximum tolerated dose (≥ 2000mg but ≤ 4000mg tablets daily). Number of paracetamol tablets and the daily average pain was noted by the subject in a subject diary every evening.

Treatment Phase (12 weeks):

At the Baseline Visit (Visit 2), following completion of all procedures and confirmation of enrollment eligibility, the subject received buprenorphine transdermal patch 5 µg/h. Subjects were titrated up to an effective and tolerated dose of study drug and used sponsor provided paracetamol as rescue analgesic therapy. Effective and tolerated dose was assessed by data recorded in CRF (e.g. adverse events) and subject's diary (pain score and number of tablets of paracetamol taken).

All subjects began treatment with a buprenorphine transdermal patch 5 µg/h and were then titrated, if necessary, to a maximum of 40 µg/h to achieve stable pain control. The first buprenorphine transdermal patch 5 µg/h dose started at the same day as the Baseline Visit.

The following dosage titration steps were followed stepwise:

- buprenorphine transdermal patch 5 µg/h
- buprenorphine transdermal patch 10 µg/h
- buprenorphine transdermal patch 15 µg/h (5 + 10)
- buprenorphine transdermal patch 20 µg/h
- buprenorphine transdermal patch 25 µg/h (5 + 20)
- buprenorphine transdermal patch 30 µg/h (10 + 20)
- buprenorphine transdermal patch 40 µg/h (20 + 20)

Advised dosage up-titration instruction:

All subjects started on buprenorphine transdermal patch 5 µg/h.

The subjects were advised to be treated for a minimum of 7 days and maximum of 14 days, with any given dose before up-titration to the next strength was considered. However, if the subject did not receive adequate analgesia and had been free of moderate/severe opioid related AE's for 4 days, the subject could be up-titrated to the next dosage step. The investigators used the above dosage titration schedule and their clinical judgment to up-titrate and/or down-titrate the subject to a dose that provided adequate analgesia with minimal rescue analgesic use. As in clinical practice, there was no pre-specified criteria dictating up or down titration of an opioid analgesic, each regimen had to be individually adjusted per subject response. Down titration, as dictated by subject tolerability, was allowed.

A subject diary was filled in every evening and the following was noted:

- BS-11.
- Number of paracetamol (rescue) taken.

Criteria for Evaluation:

Analysis Populations:

The full analysis population for efficacy analysis was defined as all subjects who received at least one dose of study drug and for whom at least one post dose observation was recorded for the primary efficacy variable.

The safety population was defined as all subjects who received at least one dose of study treatment.

The per-protocol (PP) population was a subset of the full analysis population and consists of subjects who sufficiently complied with the protocol. The criteria for defining the PP population are fully defined in the statistical analysis plan.

Efficacy Assessment(s):

Primary Efficacy Variable:

- Box Scale-11 (BS-11) pain scores (pain on average during the last seven days, mean change from Baseline to Completion (fulfilled all visits in the study).

Secondary Efficacy Variables:

- Western Ontario and McMaster Universities OA Index (WOMAC OA Index)
- European Quality of Life Health Questionnaire (EQ-5D)
- Sleep disturbance and quality of sleep questions.
- Subjects global assessment of pain relief
- Investigators global assessment of pain relief
- Incidence of rescue medication

Exploratory Efficacy Variables:

Not applicable.

Drug Concentration Measurements: Not applicable.

Bioanalytical Methods: Not applicable.

Pharmacodynamic Measurements: Not applicable.

Safety Assessments:
Safety was assessed by documenting adverse events, clinical laboratory results, vital signs and physical examinations, and recorded on the standard CRF pages and SAE data form.
At each visit the subject was asked by the Investigator/site staff for any adverse event.

For each adverse event, the following information was recorded: description of the event, date of onset, date of resolution, action taken, study drug action taken, severity of the event, seriousness of the event, outcome of the event and Investigator's assessment of relationship to study drug.

All SAE's were documented on a standard SAE form and were reported to the Sponsor within 24 hours after the first knowledge of the SAE.

Statistical Methods:

Efficacy Analyses: The primary endpoint was analysed using ANCOVA with gender, centre and baseline BS-11 score included in the model The comparison between the two age groups was performed based on the least-squares means obtained from the ANCOVA model.

Interim Analyses: Not applicable.

Safety Analyses: The number and percentage of adverse events are summarized by system organ class, MedDRA term and phase. Discontinuation details, vital signs and laboratory test are summarized descriptively.

Sample Size Rationale: The sample size was calculated on the mean change from baseline to completion in the BS-11 pain score with equivalence limits of - 1.5, the one-sided significance level 2.5% and 90 % power gives 39 per protocol subjects per age group.

Summary of results:

Efficacy results:

The buprenorphine transdermal patches had a significant effect on mean BS-11 pain scores in both age groups. Overall, the mean BS-11 pain score improved with 2.2 during the study period. 1.5 is usually taken to be clinically relevant. There was no difference between the age groups regarding the change from baseline to last visit in mean BS-11 pain score.

There was no difference between the two age groups for all WOMAC parameters except for pain. Pain was reduced more in the younger group compared to the elderly group in the PP population. A statistically significant decrease in WOMAC total score from baseline to last visit was observed in both age groups.

There was no statistically significant difference between the age groups on EQ-5D (mobility,

selfcare, usual activities, pain/discomfort) at last visit
Overall the majority of the subjects in both age groups had no problems regarding self care, usual activities and anxiety/depression.
Overall the majority of the subjects in both age groups reported problems with mobility (71%) and pain/discomfort (96%).

There was an improvement in the subjects general state of health (EQ-5D VAS) within each age group. The mean change from baseline to the end of study was 12 in the younger age group and 6 in the elderly age group.

Additional analyses were performed regarding EQ-5D index.
There were statistically significant improvements in health state both for the younger age group and for the elderly age group when analysing the change in EQ-5D index from baseline to last visit. No differences between the age groups were observed when comparing change from baseline to last visit in the EQ-5D index.

The sleep quality improved in both age groups. 61% in the younger age group rated it as "good" or "very good" at the end of the study compared to 22% at baseline. 67% in the elderly age group rated it as "good" or "very good" at the end of the study compared to 31% at baseline. The improvement in sleep quality was statically significant within each age group.
The mean number of nights woken due to pain decreased both in the younger age group (1.8) and in the elderly age group (1,3) when comparing baseline to last visit. The decrease within each age group was statistically significant. There was no statistically significant difference between the age groups.

The majority of the subjects in both age groups had either "good" or "very good" pain relief, 78% in the younger age group and 68% in the elderly age group. The buprenorphine transdermal patches were rated as better or much better compared to pre-study treatment. This was also confirmed by the investigators.

The mean daily intake of paracetamol rescue medication changed from 5.3 tablets at baseline to 2.6 at the end of the treatment period. The change was observed already after one week of study medication and didn't change much over time. There was no difference between the age groups.

The mean optimal dose was 14,5 µg/h in the younger age group and 11,3µg/h in the elderly age group. Mean time to optimal dose was 21,6 days in the younger age group and 22,1 days in the elderly age group.

Safety results:

Approximately 90% of the subjects in both age groups reported at least one AE. More AEs were reported by the younger subjects (338 AEs, 72 unique AEs) than the elderly subjects (175 AEs, 65 unique AEs). All AEs were mild or moderate and didn't require any dose reduction.

The most commonly reported AEs in both age groups were nausea, dizziness, fatigue, constipation and headache.

Patch site reaction was recorded at each visit. The majority of the subjects in both groups showed no evidence of irritation after the first week, 89 % in the younger age group and 95% in the elderly age group. At the last visit the corresponding figures were 65 % in the young age group and 88%.

5 subjects reported 10 SAEs during the study, all in the elderly age group. The majority of the SAEs were considered to be not related to the study drug except 4 SAEs (Increased ALT, Increased AST, Increased ALP, and Increased G-GT). These events were reported by the same subject.

There were no clinical important changes in vital signs or laboratory parameters from baseline to the end of study in any of the age groups.

Conclusion:
The hypothesis that the elderly age group ≥75 years was non-inferior compared to the age

group 50-60 years has been confirmed regarding change BS-11pain score. There were no significant differences between the age groups in any of the parameters investigated.
The reported adverse events were in line with the SPC and generally mild or moderate in both age groups.
The study supports the conclusions from the pharmacokinetic study, BUP1502, that no dose adjustment was needed due to age in a clinical setting.