2. SYNOPSIS

<table>
<tr><td>Name of Company:
Napp Pharmaceuticals Ltd</td><td>INDIVIDUAL STUDY TABLE</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Name of Finished Product:
BuTrans</td><td rowspan="2">Referring to Part IV of the Dossier
Volume: Page:</td></tr>
<tr><td>Name of Active Ingredient:
Buprenorphine</td></tr>
<tr><td colspan="3">Title of the Study: An open, randomised, multicentre study to compare buprenorphine transdermal delivery system (BTDS) with standard treatment in elderly subjects with OA of the hip and/or knee</td></tr>
<tr><td colspan="3">Centres: 38 active sites in the UK (3 sites did not recruit any subjects)</td></tr>
<tr><td colspan="3">Publication (Reference): None</td></tr>
<tr><td>Study Dates:
12-Apr -2006 to 21-Aug -2007</td><td>Study Status:
Completed</td><td>Phase of Development:
Phase 4</td></tr>
<tr><td colspan="3">Objectives: To evaluate the use of Buprenorphine Transdermal Delivery System compared to co-codamol (paracetamol/codeine phosphate combination treatment) in elderly osteoarthritis (OA) patients. The primary objective was to assess average daily pain intensity. Secondary and Exploratory endpoints were also measured.</td></tr>
<tr><td colspan="3">Methodology: The study was an open, randomised, parallel group, multicentre design, with centres mainly in primary care (36 of the 38 sites were General Practitioner [GP] sites). Subjects who were eligible to enter the study received treatment in accordance with the randomisation schedule.

The study consisted of a dose titration period for one to ten weeks during which the investigator titrated the subjects study medication in a stepwise fashion i.e. increased or reduced the medication by one dose level every 7 or 14 days. The Investigators were to use their clinical judgment to up or down titrate the subject's dose at the end of each titration week, or, if either the investigator or the subject were unsure as to whether optimum pain control had been achieved, the subject should have remained on the same dose level for a further week. Subjects who achieved optimum pain control then entered a 12-week assessment period.

The investigator assessed if the subject was at optimum pain control using the data recorded in the CRF and the data recorded by the subject in the diary. The investigator reviewed the following:
• number of tablets and time of dosing of NSAID (ibuprofen) for breakthrough pain
• Average daily pain score recorded on a BS-11 pain scale in the evening, before going to bed
• volunteered AEs

Visits were as follows:
screening and study entry (Titration Visit 1)
end of Titration Week 1 (Titration Visit 2)
Optional Titration visits 3-11 (at the end of weeks 2-10)
NB The titration period was a maximum of 10 weeks in which the dose of medication could be up or down titrated, or if necessary a subject may have remained on a particular dose strength for 2 weeks in order to achieve optimum pain control.
Assessment visits 12, 13, 14 at the end of assessment weeks 4, 8 and 12.
Outcome visit one month (~4 weeks) after discontinuation/completion of the study (may have been completed by telephone).</td></tr>
<tr><td colspan="3">Number of Subjects: 220 enrolled subjects (110 per group). All subjects in this study, except 4, were recruited by GP sites. The highest recruiting site, which recruited 26 subjects, was a GP site.</td></tr>
</table>

Indication and Criteria for Inclusion:

Screening Inclusion criteria

Subjects of either sex aged 65 years or above with a clinical diagnosis of osteoarthritis whose primary pain site was of the hip(s) and/or knee(s) and who reported severe osteoarthritic pain confirmed by a score of ≥ 5 on a BS-11 scale and therefore required a WHO step II analgesic medication; subjects who were taking a maximum dose of paracetamol (six to eight 500 mg tablets daily) with or without an NSAID; subjects who had not received strong opioid therapy within 6 weeks of entry into the study; subjects who were willing and able to complete quality of life questionnaires and a daily subject diary; subjects who gave written informed consent to participate in the study.

*Amendment No. 3, dated 29-Sep-2006, changed the inclusion criteria to: Subjects of either sex aged **60 years** or above with a clinical diagnosis of osteoarthritis whose primary pain site was of the hip(s) and/or knee(s) and who reported severe osteoarthritic pain confirmed by a score of ≥ 5 on a BS-11 scale and therefore required a step II medication; Subjects who were taking a maximum **tolerated** dose of paracetamol (**≥ 4** 500 mg tablets daily) with or without an NSAID.*

Screening Exclusion criteria

Subjects with any painful disease of the joints, other than osteoarthritis e.g. gout, rheumatoid arthritis, ankylosing spondylitis etc; subjects with any chronic painful condition other than osteoarthritis, likely to warrant the persistent use of escape analgesics; subjects scheduled for elective surgery of the disease site (e.g. major joint replacement surgery), or any other elective major surgery, which would have fallen within the study period; subjects recording < 5 on the BS-11 pain scale; subjects who had received an intra-articular steroid injection within six weeks of entering the study, or in whom such therapy was planned within the study period; subjects with a known allergy, hypersensitivity or other contraindication to buprenorphine or other opioids, transdermal delivery systems or patch adhesives or to NSAIDS; subjects taking COX II selective inhibitors; subjects currently taking monoamine oxidase inhibitors (MAOIs) or who had been taking MAOIs within two weeks of entering the study; subjects taking hypnotics, anxiolytics, selective serotonin re-uptake inhibitors (SSRIs) or tricyclic antidepressants whom, in the investigator's opinion, there might have been a risk of additional CNS depressant effects with the opioid components of the study medication; subjects with clinically significant respiratory depression; cardiac, hepatic or renal insufficiency; or obstructive airways disease in whom, in the opinion of the investigator, the use of opioids would have been contra-indicated; subjects with a history of asthma in whom, in the opinion of the investigator, the administration of an opioid may have precipitated an acute asthmatic attack; subjects at risk of seizures or who had a history of seizures or who were receiving concomitant anticonvulsant therapy for epilepsy or a history of convulsive disorders; subjects with a history of depression or other psychiatric disorder that in the opinion of the investigator were significant enough to exclude the subject from the study; subjects who currently abused alcohol or drugs, or had a recent history of alcohol or drug abuse or who, in the investigator's opinion, had previously demonstrated drug-seeking behaviour; subjects who had participated in a clinical research study involving a new chemical entity or an experimental drug within 30 days of study entry; subjects with evidence of raised intracranial pressure or head injury; subjects with a history of or current myasthenia gravis; subjects who, for the study period, required and could not discontinue therapy which involved direct external heat sources such as heat lamps, electric blankets, saunas, heating pads and heated water beds; subjects with any dermatological disorder at any relevant patch application site; subjects with hairy areas who could not or would not cut the hair at the patch site for proper placement of the patch; any other contraindications listed on the Summary of Product Characteristics for BTDS or Co-codamol tablets; subjects whom the investigator believed to be medically unfit to receive the study medication, or unsuitable for any other reason.

Test Treatment, Dose, and Mode of Administration:

- 5 mg (5 μg/hr) buprenorphine patch applied every 7 days, LTS Lohmann, Germany + paracetamol tablets 2 x 500 mg qds
- 10 mg (10 μg/hr) buprenorphine patch applied every 7 days, LTS Lohmann, Germany + paracetamol tablets 2 x 500 mg qds
- 20 mg (20 μg/hr) 1 x 20 mg buprenorphine patch applied every 7 days, LTS Lohmann, Germany + paracetamol tablets 2 x 500 mg qds

Reference Treatment, Dose, and Mode of Administration:

- Co-codamol tablets 8/500 (codeine phosphate 8 mg, paracetamol 500 mg) 2 qds
- Co-codamol tablets 15/500 (codeine phosphate 15 mg, paracetamol 500 mg) 2 qds
- Co-codamol tablets 30/500 (codeine phosphate 30 mg, paracetamol 500 mg) 2 qds

Duration of Treatment:

There was a titration period of one to ten weeks and an assessment period of 12 weeks followed by an outcome visit approximately 4 weeks after completion or discontinuation.

Recruitment duration was 12 months.

Treatment Schedule:

Subjects were restricted to the dose levels indicated in Table 1 and may have only changed their dose of study medication by one dose level (up or down) at a study visit.

NB during the titration period, if deemed necessary in the investigator's clinical judgment, a subject could remain on the same dose for a second week (a maximum of 14 days) before moving up to the next dose level.

Table 1: Dosing Chart

Dose Level	Buprenorphine Patch	Co-codamol
1	5 mg (5 μg/hr) + paracetamol 500 mg (2 tablets qds)	2 x 8/500 mg tablets qds
2	10 mg (10 μg/hr) + paracetamol 500 mg (2 tablets qds)	1 x 8/500 mg + 1 x 15/500 tablets qds
3	15 mg (5 mg + 10 mg patch) (15 μg/hr) + paracetamol 500 mg (2 tablets qds)	2 x 15/500 mg tablets qds
4	20 mg (20 μg/hr) + paracetamol 500 mg (2 tablets qds)	2 x 15/500 mg tablets qds
5	25 mg (20 mg + 5 mg patch) (25 μg/hr) + paracetamol 500 mg (2 tablets qds)	2 x 30/500 mg tablets qds

The maximum dose of BTDS permitted during the study was 25 mg. The maximum dose of Co-codamol that was permitted during the study was 2 x 30/500 mg tablets qds.

Subjects took their first dose of study medication on the morning of Day 1 at Dose Level 1.

Duplicate patches were made available if required.

Subjects were advised that they should have only taken their NSAID medication in the event of breakthrough pain.

Criteria for Evaluation:

Efficacy:

Efficacy Assessment(s):

Primary Measures

The primary efficacy measure was the average daily pain score recorded on a BS-11 pain scale in subject diaries every evening before going to bed.

The mean BS-11 pain scores recorded during the study were calculated for each subject during the last week of the titration period and for each two week interval of the assessment period.

Secondary Measures

Optimum method of titration: Looking at time to achieve stable pain control, length of time on anti-emetics and discontinuation of subjects in the titration period.

Escape Medication Use

All NSAID use for breakthrough pain was recorded daily by the subjects in their diaries.

Sleep Scale from the Medical Outcomes Study

This was completed by all subjects at study entry and at completion of the assessment period or discontinuation from the study.

Laxative use

All laxative use was recorded daily by the subjects in their diaries.

Exploratory Measures

WOMAC Osteoarthritis Index

This was completed by all subjects at study entry, end of titration period and either on completion of the assessment period or discontinuation from the study.

Treatment Satisfaction Questionnaire for Medication (TSQM)

To be completed by all subjects at the end of the assessment period of the study (week 12) or at discontinuation from the study.

Health status questionnaire (EuroQol EQ-5D Questionnaire)

To be completed by all subjects during the assessment period of the study at screening, visits 12 and 13 and at visit 14 or study discontinuation.

General Well-being Index

To be completed by all subjects at screening, visit 12 and at visit 14 or study discontinuation

Health Care Resource Utilization

Data on health care resource utilization were recorded in the diary by the subjects weekly.

Patch Durability

At each visit after study entry, the investigator and subject assessed the durability of the patch whilst it was being worn by the subject.

Safety:

Safety was assessed by documentation of AEs, vital signs, physical examinations and patch site assessment.

Adverse Events

The subjects' volunteered symptoms and side effects (AEs) were recorded on the standard CRF page at each visit by asking an open question. Criteria for assessing severity were ***mild***, ***moderate*** or ***severe***. Criteria for assessing causality were ***not related***, ***unlikely related***, ***possibly related***, ***probably related*** and ***definitely related.***

Serious Adverse Events

These were recorded on the standard SAE data form and reported by the Pharmacovigilance Department at NPL.

Vital Signs

Vital signs – weight, blood pressure and pulse rate were recorded at screening and on completion/discontinuation from the study.

Patch Site assessment

The responses to the subject and investigator assessments of the patch site for itchiness, erythema and oedema were summarized by dose and time as categorical data. The worst score obtained for itchiness, erythema and oedema during the study period was also summarized.

Statistical Methods:

Efficacy Analyses:

The primary efficacy variable was summarized for subjects in both the full analysis and the PP population. The PP population was the primary analysis population. All other efficacy variables were summarized for subjects in the full analysis population only.

Summaries were produced by treatment group and period/visit as appropriate unless otherwise stated. All continuous data were summarized using the following descriptive statistics: number, mean, standard deviation, median, lower and upper quartiles (if appropriate), minimum and maximum. All categorical data were summarized as the number and percentage of subjects in each category.

Primary efficacy analysis

The mean BS-11 pain scores recorded during the assessment period were calculated for each subject during the last week of the titration and each two week interval of the assessment period.

The mean BS-11 score at each interval were summarized as continuous data and analysed using a repeated measures ANCOVA model with assessment period as a repeating factor and the baseline BS-11 score as a fixed effects covariate. The overall estimated mean treatment difference and the corresponding 95% CIs were determined from this model.

SAS version 9.1 was used to summarise and analyse the data.

Secondary efficacy analysis

Optimum method of titration

The length of time to achieve stable pain control during the study was calculated for each subject and summarized as continuous data.

The length of time (number of days recorded) that subjects took anti-emetics and laxatives and the proportion of time in the study for which anti-emetics and laxatives were required by subjects were calculated and summarized as continuous data.

The number of subjects that discontinued from the study were summarized by treatment group and period of discontinuation (titration, assessment period) as categorical data.

Escape medication

The mean escape medication use (ibuprofen dose/day) during the last week of the titration period and each two week interval of the assessment period was calculated.

*Amendment no.2, dated 15 May 2006, changed the sentence above to: The mean escape medication use (ibuprofen dose/day) during the last **week** of the titration period and each two week interval of the*

assessment period was calculated.

The mean escape medication use at each interval was summarized as continuous data and analysed using a repeated measures ANCOVA model with assessment period as a repeating factor. The overall estimated mean treatment difference and the corresponding 95% CIs were determined from this model.

For the summary and analysis of the mean escape medication use in the full analysis population, missing data were imputed using the last observation carried forwards (LOCF).

Sleep scale

The responses to the sleep scale recorded at study entry and completion/discontinuation were summarized by treatment group and period. The average number of hours slept each night were summarized as continuous data and the responses to the remaining questions were summarized as categorical.

Laxative use

The length of time (number of days recorded) that subjects took laxatives and the proportion of time in the study for which laxatives were required by subjects were calculated and summarized as continuous data.

Safety Analyses: All safety variables were listed and summarized by treatment group for subjects in the safety population.

Adverse events

The subjects' volunteered symptoms and side effects (AEs) were categorised into Preferred Terms and associated System Organ Classes using the MedDRA coding system.

Treatment-emergent AEs were defined as AEs that started after the first dose of study medication or symptoms present at baseline that increased in severity after the first dose of study medication. AEs that were considered possibly, probably, or definitely related to study medication were defined as adverse drug reactions (ADRs). Treatment-emergent AEs and ADRs were assigned to a phase (titration, assessment and overall) according to their start date.

The number and percentage of subjects reporting treatment-emergent AEs and ADRs were summarised by System Organ Class, Preferred Term, and phase, and overall.

The number and percentage of subjects reporting the most common treatment-emergent AEs and ADRs were summarized by systems organ class, Preferred Term, and phase, and overall.

The number and percentage of subjects reporting the most common treatment-emergent AEs and ADRs (overall incidence greater than or equal to 10%) during the study were summarized by treatment group, study phase and severity.

Vital signs

The vital signs recorded for subjects were summarized by treatment group and study period.

Study medication

Extent of exposure was defined as the length of time between the first and last dose of study medication. Extent of exposure was summarized as continuous data. The length of time at each dose level of study medication was summarized as continuous data.

Patch site assessment

The responses to the subject and investigator assessments of the patch site for itchiness, erythema and oedema were summarized by treatment group and time as categorical data. The worst score obtained for itchiness, erythema and oedema during the study period was also summarized.

Results:

Efficacy:

Primary Efficacy Variable

Pain Scores

Analysis of the mean BS-11 pain scores at 2-week intervals during the assessment period showed that treatment with buprenorphine + paracetamol was not inferior to treatment with co-codamol and the lower limit of the 95% CI of estimated treatment difference (-0.64 to 0.60) was well within the pre-specified limits for non-inferiority.

Secondary Efficacy Variables

Escape Medication Use

Subjects in the buprenorphine + paracetamol group required an average of 0.5 to 0.8 doses of rescue medication (ibuprofen) per day, compared to an average of 1.2 to 1.4 doses per day in the co-codamol group (PP population). Analysis of escape medication use across the study period indicates a treatment difference of -0.98 (95% CI -1.55 to -0.40), which was statistically significant at the 5% level (p=0.002). Summary statistics for escape medication use in subjects aged 60 to 64 and 65 years or older showed similar results to the overall PP population.

MOS Sleep Scales

Subjects in both treatment groups showed a reduction in MOS scores for sleep disturbance during the study. An improvement in sleep adequacy was observed in the buprenorphine + paracetamol group between baseline (50.8 ± 25.35) and end of study (62.5 ± 28.26), whereas there was only a slight improvement in the co-codamol group. In addition, there was a slight improvement in the number of subjects who reported an optimal (7 to 8 hours) sleep in the buprenorphine + paracetamol group versus the co-codamol group.

Time to Optimum Pain Control

The average time to reach optimum pain control was similar in both treatment groups for the PP population (buprenorphine + paracetamol: 19.5 ± 11.95 days; co-codamol: 21.8 ± 13.76 days). However, the median values show that 50% of subjects in the buprenorphine + paracetamol group reached optimum pain control in 2 weeks (14 days) versus almost 3 weeks (20.5 days) for 50% of subjects in the co-codamol group.

Laxative Use

Fifty percent of subjects in both treatment groups did not require any laxatives during the study (median laxative use = 0). The median and inter-quartile range for the number of days and percentage of days with laxative use were similar for both treatment groups in the PP population. However, in the full analysis population, laxatives were required for a slightly longer period of time in the co-codamol group versus the buprenorphine + paracetamol group. The percentage of days with laxative use was also slightly higher in the co-codamol group.

Safety: Four subjects reported 6 SAEs during the study. All of the SAEs were considered to be not related or unlikely related to study drug. Other significant AEs (AEs resulting in discontinuation, dose reduction or additional therapy) occurred in both treatment groups. The number of subjects reporting AEs which resulted in a dose reduction or the administration of additional therapy was similar in both treatment groups, while the number of subjects who discontinued the study due to AEs was slightly higher in the buprenorphine + paracetamol group, compared to the co-codamol group. The most common reason for any significant event in either treatment group was an AE in the Gastrointestinal Disorders System Organ Class.

Incidence of Deaths, Other Serious Adverse Events, and Other Significant Events: Safety Population

	Buprenorphine + paracetamol (N = 110)	**Co-codamol (N = 109)**
Category[a]	n (%)	n (%)
Deaths	0	0
Serious adverse event(s)[b]	3	1
Other significant events		
Adverse events leading to discontinuation	38 (34.5%)	24 (22.0%)
Adverse events requiring reduction in dose of study drug	5 (4.5%)	5 (4.6%)
Adverse events requiring significant additional therapy	49 (44.5%)	55 (50.5%)

[a]A subject may have had more than 1 other significant event; subjects with other significant events may have also had a serious adverse event or died.
[b]Includes subjects who died because of a serious adverse event.
Cross-reference: Tables 14.3.6, 14.3.7, 14.3.7.2, Appendix 16.2.7

Vital sign changes outside the normal range were isolated and not considered clinically important by the Investigator. Based on the vital sign data available in this study, no vital sign abnormality was directly attributable to study drug. The mean values for systolic blood pressure, diastolic blood pressure and pulse rate were within the normal range at baseline and end point in all treatment groups. There were no clinically important changes in mean vital signs from baseline to end point for any treatment group.

Of the subjects that received buprenorphine patches, fewer than 10% reported moderate or severe skin reactions (erythema, itching, oedema) at the patch site at the end of the study or at the outcome visit. Seventy-one percent of subjects did not report any erythema. Very few subjects reported itchiness or oedema at the patch site. The Investigators' assessment of the patch site at the end of the study or at the outcome visit was similar to the subject's assessment of the patch site.

The subjects' assessment of the patch site immediately after the patch was removed showed that severe skin reactions occurred with fewer than 1% of patches worn. Although mild erythema was reported on removal of 17% of patches, mild erythema was reported for only 8% of patches at 24 hours after removal, suggesting that the erythema was short-lived.

Conclusions:

- Treatment with buprenorphine + paracetamol was not inferior to treatment with co-codamol and the lower limit of the 95% CI of treatment difference (-0.64 to 0.60) was well within the pre-specified limits for non-inferiority.

- Mean BS-11 pain scores improved at least 3 box points by the end of the titration period in both the buprenorphine + paracetamol and co-codamol groups. An improvement of 2 box points is usually taken to be clinically significant. This improvement was maintained throughout the 12-week assessment period in both treatment groups.

- Fewer subjects in the buprenorphine patch + paracetamol treatment group (10.2%) withdrew due to lack of efficacy in comparison with the co-codmaol treatment group (25%).

- Subjects receiving buprenorphine + paracetamol used approximately one dose less per day of escape medication, compared to the subjects receiving co-codamol. This difference was statistically significant. A cumulative reduction of oral NSAID use in this elderly population could reduce the incidence of potentially serious gastrointestinal side-effects.

- Subjects over 65 years of age showed no difference compared to the overall study population (age >60 years) in their response to treatment with buprenorphine + paracetamol, as indicated by their BS-11 pain scores and escape medication use.

- Subjects in both treatment groups showed an improvement in their sleep patterns as demonstrated by a reduction in MOS scores for sleep disturbance during the study. In addition, there was a slight improvement in the number of subjects who reported an optimal (7 to 8 hours) sleep in the buprenorphine + paracetamol group versus the co-codamol group.

- Fifty percent of subjects in the buprenorphine + paracetamol group reached optimum pain control in 2 weeks versus almost 3 weeks for 50% of subjects in the co-codamol group. This demonstrates that titration to pain relief with a 7-day buprenorphine patch can be as effective as titration with an oral pain medication taken 4 times a day.

- Less than 10% of subjects were using the highest buprenorphine patch strength (25 µg/h + 500 mg paracetamol, four times daily) at the end of the treatment phase, compared to 34% of subjects who were taking the highest co-codamol dose (60/500 mg four times daily) at the end of the treatment phase.

- Fifty percent of subjects in both treatment groups did not require any laxatives during the study. However, in the full analysis population, laxatives were required for a slightly longer period of time in the co-codamol group versus the buprenorphine + paracetamol group. The percentage of days with laxative use was also slightly higher in the co-codamol group.

- The effect of whether prophylactic anti-emetic therapy for the first 7 days of treatment could minimise discontinuation was investigated. Although nausea was the most frequently reported AE leading to discontinuation in the BTDS group (15%) there was no clear pattern in the onset; a number of subjects reported nausea as early as Day 2 whilst others didn't report it until after the third week (day 21). With regard to the use of anti-emetic medication and the onset of nausea/vomiting, although some subjects reporting nausea had not taken anti-emetics, some had escaped nausea symptoms for 3 weeks. The patient diaries and returned clinical trial supplies indicated that there was a considerable number of patients who did not take prophylactic anti-emetics.

- The concomitant medications taken by subjects during the study were mainly taken for pre-existing conditions typical of the patient population investigated in this study, i.e. patients over 60 years of age with a diagnosis of osteoarthritis. A 7-day buprenorphine patch that removes or reduces the need for daily pain medication may help to reduce the overall number of medications that elderly patients need to take and therefore benefit their quality of life.

- The exploratory analyses showed little difference between the treatment groups, as both groups of subjects showed improvements in the WOMAC Osteoarthritis Index, similar global treatment satisfaction scores and similar EuroQol EQ-5D questionnaire responses.

- There were no deaths during the study. Four subjects reported 6 SAEs during the study. All of the SAEs were considered to be not related or unlikely related to study drug.

- Previous clinical trial studies conducted on BTDS suggested that subjects experienced most adverse events during the initial titration period. This was especially due to nausea and/or vomiting for the BTDS treatment group. Therefore, this trial investigated whether initial adverse events could be minimised by encouraging a slow titration with a minimum time interval of 7 days before increasing to the next dose level. The results suggest that most patients showed little relationship between the speed of dose titration and the incidence of adverse effects, including trial discontinuation.

- The most common reason for any significant event in either treatment group was an adverse event in the Gastrointestinal Disorders System Organ Class.

- There were no clinically important changes in mean vital signs from baseline to end point for any treatment group.

- Very few subjects (≤8 subjects) reported skin problems with their buprenorphine patch. Severe skin reactions occurred with fewer than 1% of patches worn. Although mild erythema was reported on removal of 17% of patches, mild erythema was reported for only 8% of patches at 24 hours after removal, suggesting that the erythema was shortlived.

- The low incidence of skin reactions observed in this study, indicate that the 7-day buprenorphine patch is suitable for use on elderly skin, which may be thinner and more translucent than the skin of younger subjects.

Date of the Report: 26 Mar 2008