2 SYNOPSIS

Name of Sponsor/ Company: Reckitt Benckiser Healthcare (UK) Ltd	**Individual Trial Table Referring to Part of the Dossier**	**(For National Authority use only)**
Name of Finished Product: N/A	**Volume:**	
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Title of Trial: A randomised, double blind, crossover pilot study of intravenous buprenorphine versus intravenous buprenorphine/naloxone in patients with chronic pain.

Investigator(s): [redacted]

Trial Centre(s): This was a single centre trial at Leeds Pain Management Service, Seacroft Hospital and St James's University Hospital, Leeds, UK

Publication (reference): None as of the date of this Final Report

Studied Period: 9 months **Date first subject enrolled:** 19 November 2007 **Date last subject completed:** 1 July 2008	**Phase of Development:** III

Objectives: The main objective of this study was to further investigate the efficacy and safety of buprenorphine in the treatment of chronic pain compared to buprenorphine/naloxone.

Methodology: Patients had the purpose of this study, the study procedures and their responsibilities fully explained and were asked to read a Patient Information Sheet. Each patient was invited to attend a screening visit following this (approximately one week later). At this visit the patient attended the Out-Patients Department at Seacroft Hospital, and if they agreed to participate in the trial, written informed consent was obtained.

At the screening visit, the patient's eligibility was checked by conducting the following assessments:

- Demography including pain assessment (pain diagnosis, duration, VAS, SF-MPQ, BPI)
- Vital signs including blood pressure, pulse and respirations per minute
- Medical history
- Current medical conditions
- Concomitant medications
- Maximum blood sample of 20 mls for clinical chemistry and haematology (that included electrolytes, serum creatinine, AST/ALT, alkaline phosphatase, bilirubin, haemoglobin, white blood cell count)
- Female patients of childbearing potential were required to take a urine pregnancy test
- Patients were given thorough training by either the investigator or research nurse on how to complete the scales correctly.

On each treatment day patients attended the in-patient Day Unit at St James's University Hospital, Leeds. They were assessed by the Research Nurse and Study Doctor to ensure that they were still eligible for the study. Each patient received a single IV dose of either buprenorphine (0.3mg) or buprenorphine/naloxone (0.3/0.02mg) (as randomised) administered by slow bolus via a syringe driver over 5 minutes. This was administered under double-blind conditions.

There was a two day pre-treatment/washout period prior to each treatment during which patients were required to take a stable dose of regular step II analgesia. Sustained-release formulations of opioid analgesics and tramadol were excluded. At the end of the pre-treatment period the patient attended the day-unit as an in-patient for the treatment day and, subject to continuing to meet the inclusion/exclusion criteria, were randomised to treatment the

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same day.

Prior to the second treatment day patients underwent another two day pre-treatment period with the same assessments as for the first pre-treatment period.

Patients did not take their step II analgesic after midnight on Day 7 and Day 15 (immediately before the treatment days). Breakthrough analgesia was available in the form of paracetamol during this time.

No more than two patients were treated at any one time.

There was a washout period of at least seven days between each treatment day.

A follow-up visit took place at Seacroft Hospital within seven days of the final treatment day.

Number of Subjects: 20 patients were randomised and all completed the study

Inclusion criteria

- Written informed consent.
- Male or female patients aged 18 years or over.
- Patients with a recognised chronic pain condition greater than three months duration that had been diagnosed by a pain management specialist.
- Patients with moderate to severe chronic pain (defined as a minimum of 40 mm pain score on the 100mm pain visual analogue scale at screening and a minimum average daily pain score of 4 on an 11-point Likert scale (0, no pain; 10, worst pain ever experienced) during pre-treatment.
- Adequate renal function (serum creatinine females <130 mmol/l: males <150 mmol/l).
- Liver enzymes (AST or ALT) less than twice the upper limit of normal. Alkaline phosphatase less than twice the upper limit of normal.
- Bilirubin within the normal range.
- Patients stabilised on regular doses of step II analgesics for at least 2 weeks prior to the pre-treatment period of the study. Regular doses of analgesia had to be continued during the study period (except for the two treatment days).

Exclusion criteria

- Woman of childbearing potential, who were pregnant or lactating, seeking pregnancy or failed to take adequate contraceptive precautions, i.e. an oral contraceptive, an approved hormonal implant, an intrauterine device or condoms/diaphragm and spermicide). A woman of childbearing potential was defined as any female who was less than two years post-menopausal or had not undergone a hysterectomy or surgical sterilisation, e.g. bilateral tubal ligation, bilateral ovariectomy (oophorectomy).
- Patients receiving sustained-release formulations of opioid analgesics or tramadol.
- Patients who had a history of experiencing intolerable opioid analgesic side effects.
- Patients who were receiving tricyclic antidepressants, anticonvulsants, membrane stabilisers or steroids for the pain if the doses had not been stable for the two weeks prior to the pre-treatment period of the study or if doses were likely to change during the study.
- Patients who are receiving monoamine oxidase inhibitors, phenobarbital, carbamazepine, phenytoin,

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rifampicin, gestodene, troleandomycin, ketonazole, norfluoxetine, ritonavir, indinavir or saquinavir.

- Abnormal serum electrolytes, which in the investigators opinion would exclude the patient from this study
- Haemoglobin outside the normal limits and white blood cell count below the lower limit of normal or above 12 x 10^9/l.
- Patients who had anxiety or depression to such a degree that the investigators judged that participation in the study would have been detrimental to their mental health.
- Patients who were unable to understand and complete assessment questionnaires in English and those unable to complete VAS scales.
- Concurrent surgery, radiotherapy, chemotherapy or nerve blocks and those who have received this treatment four weeks prior to the study.
- Patients who were receiving, or had received buprenorphine based analgesia in the last 14 days.
- Patients who have been in another clinical study within the last 3 months.
- Patients with a previous history of allergy or intolerance to buprenorphine, naloxone or paracetamol.
- Patients who have been previously randomised into the study.
- Patients who had a past history of impaired respiratory function or who, in the opinion of the investigator, had clinically impaired respiratory function

Test Product:

Buprenorphine 0.3mg (batch number 4996) or buprenorphine 0.3mg + naloxone 0.02mg ampoule (batch number 5031) for a single IV administration over 5 minutes (day 8). On day 16 the patient crossed over to receive the other medication in the same manner.

Duration of Treatment: Two single doses on separate days. Each patient was involved in the study for 18 days

Reference Therapy:

The study medication was supplied in 1ml ampoules containing 0.3 mg buprenorphine or 0.3mg buprenorphine + 0.02mg naloxone.

Dose / treatment schedule

Patients received a single dose of IV buprenorphine or buprenorphine/naloxone in a randomised, double-blind, crossover manner according to the randomization list generated by Reckitt Benckiser (RB).

Concomitant medication

Patients could not commence any new drug therapy throughout the study period. Patients could continue to take their concomitant analgesia throughout the study period except on treatment days. Patients were allowed to continue their antidepressant, anticonvulsant or non-steroidal anti-inflammatory (NSAID) medication providing the treatment was initiated at least 2 weeks prior to commencing the study and was on a stable dose.

Patients could not receive sustained-release formulations of step II analgesics or tramadol from the start of the

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pre-treatment period until the end of the study.

Criteria for Evaluation:

Efficacy:

Primary Efficacy Analysis Endpoint

The primary endpoint for this study was AUC (0-6h) for VAS for pain on the two treatment days.

Secondary Efficacy End-points

- Maximum pain on the VAS for pain during the six hours post-dosing
- Change from pre-dose in VAS for pain at 1, 2, 3, 4, 5 and 6 hours post-dosing
- Pain relief as measured on a 6-point scale at six and 24 hours post dosing
- Investigator global impression of change on a 7-point scale at the end of each treatment phase
- Patient global impression of change on a 7-point scale at the end of each treatment phase
- Number of doses of breakthrough medication (paracetamol) taken during each treatment phase
- Amount of sleep interference caused by pain on a 11-point Likert scale during the night following treatment
- Sensory Pain Rating Index from the SF-MPQ scale at the end of each treatment phase
- Affective Pain Rating Index from the SF-MPQ scale at the end of each treatment phase
- Total Pain Rating Index from the SF-MPQ scale at the end of each treatment phase
- Present Pain Intensity-VAS from the SF-MPQ scale at the end of each treatment phase
- Evaluative overall intensity of total pain experience on a 6-point scale from the SF-MPQ scale at the end of each treatment phase
- Worst pain as measured within the BPI at the end of each treatment phase
- Least pain as measured within the BPI at the end of each treatment phase
- Average pain as measured within the BPI at the end of each treatment phase
- Pain right now as measured within the BPI at the end of each treatment phase
- Percentage pain relief as measured within the BPI at the end of each treatment phase
- How pain has interfered with the patient's general activity as measured within the BPI at the end of each treatment phase
- How pain has interfered with the patient's mood as measured within the BPI at the end of each treatment phase
- How pain has interfered with the patient's walking ability as measured within the BPI at the end of each treatment phase
- How pain has interfered with the patient's normal work as measured within the BPI at the end of each

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treatment phase

- How pain has interfered with the patient's relations with other people as measured within the BPI at the end of each treatment phase
- How pain has interfered with the patient's sleep with other people as measured within the BPI at the end of each treatment phase
- How pain has interfered with the patient's enjoyment of life with other people as measured within the BPI at the end of each treatment phase
- Change from screening to post-study follow-up in Sensory Pain Rating Index from the SF-MPQ scale
- Change from screening to post-study follow-up in Affective Pain Rating Index from the SF-MPQ scale
- Change from screening to post-study follow-up in Total Pain Rating Index from the SF-MPQ scale
- Change from screening to post-study follow-up in Present Pain Intensity-VAS from the SF-MPQ scale
- Change from screening to post-study follow-up in evaluative overall intensity of total pain experience on a 6-point scale from the SF-MPQ scale

Safety:

Safety and tolerability was assessed in terms of the overall proportion of subjects with AEs after each treatment and changes in vital signs during the six hours post-dosing.

Statistical Methods:

All patients who took the study medication were included in the statistical analysis. As this was a pilot study no per-protocol analysis was performed.

Normality assumptions were evaluated by an examination of the residual plots and the Shapiro-Wilk test of normality. Depending on the degree of departure from these assumptions, an alternate nonparametric approach could have been used for supportive purposes.

The primary efficacy endpoint (AUC (0-6h) for VAS for pain) was analysed via a hierarchical analysis of covariance model with factors for treatment, treatment phase, treatment order ("carryover") and patient within treatment order and a covariate for pre-dose value. This model was also used for the following variables:

- Maximum pain on the VAS for pain during the six hours post-dosing
- Change from pre-dose in VAS for pain at 1, 2, 3, 4, 5 and 6 hours post-dosing
- Change from pre-dose in Sensory Pain Rating Index from the SF-MPQ scale at the end of each treatment phase
- Change from pre-dose in Affective Pain Rating Index from the SF-MPQ scale at the end of each treatment phase
- Change from pre-dose in Total Pain Rating Index from the SF-MPQ scale at the end of each treatment phase
- Change from pre-dose in Present Pain Intensity-VAS from the SF-MPQ scale at the end of each treatment phase
- Change from pre-dose in Evaluative overall intensity of total pain experience on a 6-point scale from the SF-MPQ scale at the end of each treatment phase.

The following variables were analysed via a hierarchical analysis of variance model with factors for treatment, treatment phase, treatment order ("carryover") and patient within treatment order:

- Pain relief as measured on a 6-point scale at six and 24 hours post dosing
- Investigator global impression of change on a 7-point scale at the end of each treatment phase
- Patient global impression of change on a 7-point scale at the end of each treatment phase
- Amount of sleep interference caused by pain on an 11-point Likert scale during the night following treatment.

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The following variables were analysed via a hierarchical analysis of covariance model with factors for treatment, treatment phase, treatment order ("carryover") and patient within treatment order and a covariate for screening value:

- Worst pain as measured within the BPI at the end of each treatment phase
- Least pain as measured within the BPI at the end of each treatment phase
- Average pain as measured within the BPI at the end of each treatment phase
- Pain right now as measured within the BPI at the end of each treatment phase
- Percentage pain relief as measured within the BPI at the end of each treatment phase
- How pain has interfered with the patient's general activity as measured within the BPI at the end of each treatment phase
- How pain has interfered with the patient's mood as measured within the BPI at the end of each treatment phase
- How pain has interfered with the patient's walking ability as measured within the BPI at the end of each treatment phase
- How pain has interfered with the patient's normal work as measured within the BPI at the end of each treatment phase
- How pain has interfered with the patient's relations with other people as measured within the BPI at the end of each treatment phase
- How pain has interfered with the patient's sleep with other people as measured within the BPI at the end of each treatment phase
- How pain has interfered with the patient's enjoyment of life with other people as measured within the BPI at the end of each treatment phase.

The following variables were analysed via paired t-tests:

- Change from screening to post-study follow-up in Sensory Pain Rating Index from the SF-MPQ scale
- Change from screening to post-study follow-up in Affective Pain Rating Index from the SF-MPQ scale
- Change from screening to post-study follow-up in Total Pain Rating Index from the SF-MPQ scale
- Change from screening to post-study follow-up in Present Pain Intensity-VAS from the SF-MPQ scale
- Change from screening to post-study follow-up in evaluative overall intensity of total pain experience on a 6-point scale from the SF-MPQ scale.

The number of patients with adverse events on each treatment was reported by primary system organ class, preferred term, severity and relationship to study medication according to MedDRA Version 11. The differences between the two treatments in the proportion of patients with adverse events were compared by McNemar's test.

Changes from pre-dose to 0.25, 0.5, 0.75, 1, 2, 3, 4, 5 and 6 hours post dose in systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate and blood-oxygen saturation were analysed via a hierarchical analysis of covariance model with factors for treatment, treatment phase, treatment order ("carryover") and patient within treatment order and a covariate for pre-dose value.

Changes from pre-dose to 1, 2, 3, 4, 5 and 6 hours post dose in the visual analogue assessments of degree of sedation and level of nausea were analysed using the same hierarchical analysis of covariance model as used for the vital signs.

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SUMMARY & CONCLUSIONS

EFFICACY RESULTS:

Twenty subjects were recruited, 10 within each treatment sequence. Age ranged from 22 to 81 years with a mean age of 48.3 years. All subjects were Caucasian with 75% of subjects female. The mean time since diagnosis was 12.5 years with range 1 to 40 years. Ten subjects were experiencing back/lumbar pain/injury, three subjects had neuropathic pain, two had osteoarthritis and one each had head pain, osteomyelitis, shoulder pain, spinal stenosis and spondylitic myelopathy. The mean present pain intensity at screening measured on a 100mm VAS with endpoints 0mm = no pain and 100mm = worst possible pain was 77.1mm.

The primary efficacy endpoint was the AUC (0-6h) for the VAS for pain. This was analysed via hierarchical ANCOVA. Although the term for treatment was not statistically significant (p=0.71), the terms for pre-dose value (p=0.013), treatment phase (p=0.04) and treatment order (p=0.04) were all statistically significant. The least square (LS) means from this model were 43.8 mm and 45.4 mm for buprenorphine alone and buprenorphine+naloxone respectively. As a result of the significant order term, the period 1 data was analysed separately using a standard one-way ANCOVA model with a factor for treatment and pre-dose pain as a covariate. For this model neither the pre-dose value (p=0.15) nor the factor for treatment were statistically significant (p=0.06). The LS means from this model were 31.1 mm and 50.2 mm for buprenorphine alone and buprenorphine+naloxone respectively. Data from period 2 alone were not formally analysed, the raw means from this phase were 59.6 mm and 37.5 mm for buprenorphine alone and buprenorphine+naloxone respectively.

With respect to the mean present pain profile, treatment differences were small with a rapid reduction of pain during the first hour post-dosing and then a plateau in terms of pain level was seen from two to six hours post-dosing. Mean reductions in pain were highest at three hours for buprenorphine alone (-40.9 mm) and at four hours post-dose for buprenorphine+naloxone (-34.4 mm). As the treatment order term was statistically significant at the 10% level in four out of six by time point analyses, the period 1 data for this variable was analysed separately. Mean pain reductions within this phase were much larger for the group receiving buprenorphine alone with statistically significant differences at two (p=0.04) and three (p=0.03) hours post-dosing.

For secondary efficacy variables there was no real evidence of any treatment effect during the study, however for a substantial number, there was a statistically significant treatment order effect. Subjects randomised to receive buprenorphine + naloxone first reported much higher pain levels and thus when the data was analysed on a per period basis, mean pain levels heavily favoured buprenorphine in period 1 with the opposite true in period 2. Although the treatment differences seen in period 1 were undoubtedly clinically significant, there was a lack of statistical power due to the small treatment sequence sizes, consequently the only differences that reached statistical significance were for the change from pre-dose in VAS for present pain at two and three hours post-dose and the patient's global impression of change at six hours.

SAFETY RESULTS:

Nineteen (95%) subjects reported a total of 57 adverse events after dosing with buprenorphine alone compared to 17 (85%) subjects who reported 63 events after dosing with buprenorphine + naloxone. Overall, no severe events were reported, 11 events were graded as moderate (seven after treatment with buprenorphine and four following treatment with buprenorphine + naloxone). Eighty-two percent of events following buprenorphine treatment were regarded as definitely related to treatment compared to 81% following buprenorphine+naloxone treatment.

Only one serious adverse event was reported; overnight hospitalisation to investigate a probable retention of urine 4.5 hours after receiving buprenorphine + naloxone (first phase treatment).

There were larger mean decreases in systolic blood pressure after treatment with buprenorphine+naloxone; the difference between the treatments at six hours post-dose was statistically significant (p=0.004). Mean increases in diastolic blood pressure were higher when the subjects were treated with buprenorphine alone; the difference between the treatments at three hours post-dose was statistically significant (p=0.04). There were greater falls in mean respiration rate on buprenorphine alone, with the difference at 45 minutes being statistically significant (p=0.04). There were mean decreases compared to pre-dose on both treatments in terms of blood-oxygen saturation. At three hours the difference between the two treatments was statistically significant (p=0.02) with

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subjects treated with buprenorphine+naloxone having the larger mean decrease. There were no statistically significant differences between treatments in terms of heart rate, degree of nausea and level of sedation.

CONCLUSION:

For both buprenorphine alone and buprenorphine + naloxone, the profile of analgesic effects was in accordance with previous studies with intravenous buprenorphine showing a rapid onset of analgesia, peaking at 2-3 hours and a duration beyond 6 hours based on the overall results.

There was no real evidence of any overall treatment effect during the study. However, for a substantial number of the efficacy variables including the primary measure (AUC (0-6h) for the VAS for pain) there was a statistically significant treatment order effect. Subjects randomised to receive buprenorphine + naloxone first reported much higher pain levels and thus when the data was analysed on a per period basis, mean pain levels heavily favoured buprenorphine in period 1 with the opposite true in period 2. The results seen in period 1 may have been influenced by anxiety – subjects having to spend a day in hospital and receiving analgesia by the intravenous route. However there is no reason to expect that this would have a differential effect on the two treatments.

Although numerically fewer subjects experienced adverse events during treatment with buprenorphine + naloxone (17 subjects, 63 events) compared with buprenorphine (19 subjects, 57 events), this is unlikely to represent a real difference between the treatments.

The one serious adverse event that was reported (probable retention of urine 4.5 hours after receiving buprenorphine + naloxone, lasting 20.5 hours and requiring hospitalisation) is a recognised adverse reaction to any opioid treatment.

There were consistent decreases in respiration rate for both treatments throughout the 6-hour period. Although there were greater falls with buprenorphine alone, with the difference at 45 minutes being statistically significant ($p=0.04$), the mean changes were small (less than 1 breath/minute) and not of clinical significance

In line with the small changes in respiration rate there were consistent mean decreases in transcutaneous oxygen saturation throughout the 6-hour period compared to pre-dose with both treatments. At three hours the difference between the two treatments was statistically significant ($p=0.02$). The maximum mean decrease was 2% and was not clinically significant.

There were consistent increases in nausea as assessed by visual analogue scale. These were numerically worse at all timepoints with buprenorphine alone but the differences between treatments did not achieve statistical significance. The study included a high proportion of female subjects who are known to be rather more sensitive to the emetic effects of opioids.

There were consistent increases in sedation as assessed by visual analogue scale throughout the 6-hour period with peak effects at 2 hours for both treatments but no statistically significant differences between them.

Overall the study showed a typical pattern of effects of an opioid analgesic but failed to demonstrate a clear difference between buprenorphine and buprenorphine + naloxone.

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