2 SYNOPSIS

Name of Sponsor/ Company: Reckitt Benckiser	**Individual Trial Table Referring to Part of the Dossier**	**(For National Authority use only)**
Name of Finished Product: Suboxone®	**Volume:**	
Name of Active Ingredients: Buprenorphine/naloxone	**Page:**	
Title of Trial: A multicentre, randomised, open-label, active-controlled trial of the effectiveness of buprenorphine/naloxone in reducing intravenous buprenorphine misuse in France		
Co-ordinating Investigator: [redacted] Centre de soins spécialisé aux toxicomanes (CSST), [redacted]		
Trial Sites: This study was conducted in 20 active treatment addiction centres in France.		
Publication (reference): None		
Studied Period: **Date first subject enrolled:** 15 Sep 2009 **Date last subject completed (last subject last visit):** 02 Apr 2012		**Phase of Development:** IV

Objectives:

Primary Objective

The primary objective of this trial was to establish the effectiveness of buprenorphine/naloxone (Suboxone®) in reducing intravenous misuse of buprenorphine (Subutex®) in opioid-dependent subjects receiving buprenorphine maintenance therapy in France.

Secondary Objectives

- To demonstrate the efficacy of buprenorphine/naloxone in reducing use of opioids and other illicit or unprescribed drugs.
- To determine effects experienced by subjects injecting the study drug.
- To identify baseline subject characteristics associated with subsequent reduction of buprenorphine misuse.
- To further document the safety of buprenorphine/naloxone.

Methodology:

This was a phase IV, national (France), multicentre, randomised, open-label, comparative (buprenorphine/naloxone vs. buprenorphine) trial in parallel groups of subjects. This trial involved subjects treated for opioid dependence with buprenorphine for at least 3 months prior to inclusion, who misused buprenorphine intravenously at least four times a week.

Subjects who met inclusion/exclusion criteria at the Inclusion Visit (Day -7) were required to self-report intravenous misuse of prescribed buprenorphine in a daily diary. The Investigator had no access to the data collected in the diary. The baseline value for each subject was the total number of injections in the week of Day -7 to Day -1. Investigators had the discretion to allow a further week prior to randomisation to provide a diary if this was not done at Day 0.

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On Day 1, enrolled subjects were randomly (1:1) assigned to receive either buprenorphine or buprenorphine/naloxone for 3 months (Day 1 to Day 84) commencing at the same dose of buprenorphine as they were receiving immediately prior to the study.

During the first 5 days (Day 1 to Day 5 ± 2), the need for adjustment of buprenorphine/naloxone dosage was evaluated by daily telephone interviews conducted by the Investigator or designee. If adjustment was needed, subjects had to return to the centre to receive the appropriate treatment. Adjustment was done in accordance with the Summary of Product Characteristics (SmPC). Subsequent adjustment could also be performed during the remainder of the trial.

During this randomised treatment period (Day 1 to Day 84), take-home study drugs were provided each week and clinical visits were planned monthly. Throughout this period, subjects were required to document intravenous misuse of the study drug in a daily diary.

At the Inclusion Visit and at the end of the randomised treatment period (Day 84), subjects were screened for hepatitis C virus (HCV), unless their HCV status was known and documented. Hepatitis C virus positive subjects were referred to specialised facilities for complete diagnosis and, if required, HCV treatment was provided as part of standard care. HCV treatment was not a part of this trial.

Subjects assigned to buprenorphine/naloxone had the option to continue this treatment for an additional 9 months. During this optional treatment period, visits for safety purposes were to be carried out every 3 months.

The anticipated duration of the trial was approximately 9 months from screening the first subject until completion of the final subject's randomisation period. The actual duration of the trial was 3 years due to slow recruitment. The recruitment period was expected to be 6 months. The duration of the trial for an individual subject was 13 weeks which included the 3-month randomised treatment period. The duration of optional treatment period was a further 9 months for those subjects who chose to continue to receive buprenorphine/naloxone.

The Investigator was to inform subjects that they could not participate in another trial within 1 month after the end of their participation in this trial.

Subjects were compensated financially to complete trial assessments

It was planned that 270 subjects (135 in each arm) would be enrolled in up to 20 addiction treatment centres in France, with each centre enrolling approximately 14 subjects. The study was terminated due to slow enrolment after a total of 158 subjects (79 in each arm) were enrolled in 20 centres.

Number of Subjects: **Planned:** 270 (135 in each arm)

Actual: 158 (79 in each arm)

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Diagnosis and Main Criteria for Inclusion:

Subjects had to meet all the following inclusion criteria to be eligible for enrolment in the trial:

1) Male or female opioid-dependent outpatient aged 18 years or older,
2) Women of childbearing potential must have had a negative urine pregnancy test result at the Inclusion Visit (test under supervision of the Investigator or designee),
3) Women of childbearing potential (WOCP) must have used an effective birth control method for the duration of the study. WOCP had to be postmenopausal or must have been surgically sterile (hysterectomy and/or bilateral oophorectomy)
   Note: In the event of pregnancy, the subject was to be discontinued from the study and followed up by the Investigator until completion of pregnancy or until pregnancy termination, and the Investigator was to notify the Sponsor of the outcome.
4) On buprenorphine (Subutex® or generic buprenorphine) maintenance therapy at a minimum daily dose of 2 mg/day for at least 3 months prior to inclusion,
5) Declared buprenorphine intravenous misuse at least four times/week and showed needle marks,
6) Willing to stop or reduce buprenorphine intravenous misuse,
7) Having received oral and written information about the trial, and provided written informed consent prior to admission to this trial.

Subjects presenting with any of the following criteria were not included in the trial:

1) Pregnant or breast-feeding,
2) Contraindication or history of hypersensitivity to buprenorphine, naloxone or to any excipient of Suboxone® or Subutex®,
3) Any medical or psychiatric condition which in the opinion of the Investigator would make participation difficult or unsafe,
4) Participating in another trial,
5) Subjects in the exclusion period of the "Fichier National des personnes qui se prêtent à des recherches biomédicales" (National Index of persons participating in biomedical researches, or National Index of volunteers).

Test Product:

Buprenorphine/naloxone (Suboxone®) sublingual tablets

Duration of Treatment:

The duration of the trial for an individual subject was 13 weeks which included the 3-month randomised treatment period. The duration of optional treatment period was a further 9 months for those subjects who chose to continue to receive buprenorphine/naloxone.

Reference Therapy:

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Buprenorphine (Subutex®) sublingual tablets		

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Criteria for Evaluation:

Efficacy:

Primary efficacy variable

- The primary efficacy variable is the percentage of subjects achieving a 30% reduction in the average weekly number of study drug injections during the post-baseline period (randomised treatment period (Day 1 to Day 84 inclusive)) as compared to the baseline period (pre-randomisation period (Day -7 to Day -1)).

Secondary efficacy variables

- The secondary efficacy variables are as follows:
    - Average number of injections of study drug between Day 1 and Day 84 inclusive;
    - Percentage of subjects who stopped injecting the study drug. Subjects were considered to have stopped injecting the study drug if they reported no injection of the study drug in the last 2 (or more) weeks of follow-up. For subjects with incomplete follow-up, the criterion was evaluated on the last two consecutive returned weekly diaries, excluding the first 2 weeks of follow-up;
    - Severity of addiction on Day 84, as assessed by the Addiction Severity Index (ASI);
    - Severity of opiate withdrawal symptoms on Days 28, 56 and 84, as assessed by the objective opiate withdrawal scale (OOWS) and the subjective opiate withdrawal scale (SOWS);
    - Factors associated with subsequent reduction in the number of injections of study drug. The following factors were considered: demographics; addiction history, psychiatric comorbidities and ASI composite score.
- **Safety variables:** Adverse events (AEs) and serious adverse events (SAEs), coded using MedDRA dictionary version 11.0 and validated by a physician.

Statistical Methods:

Analysis cohorts:

Intent-to-treat: All randomised subjects with at least one efficacy assessment. Per protocol (PP): All subjects having received at least one dose of the study drug, with no major violation of the study protocol. Major violations were defined during the review of the study data and

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described in the statistical analysis plan (SAP). Safety: All subjects having received at least one dose of the study drug.

Baseline characteristics of participants are described for the ITT cohort. All efficacy analyses were performed using the ITT cohort. Safety analyses were performed using the safety cohort.

Descriptive statistics are presented by treatment group. Qualitative variables are described by number and percentage of subjects in each category. Quantitative variables are described using mean, standard deviation, median, minimum and maximum.

Qualitative variables are compared between the two treatment groups using chi-square tests. Quantitative variables for the baseline period and post-baseline periods are compared between the two treatment groups using t-tests, while change from baseline is analyzed using an Analysis of Covariance (ANCOVA) model with treatment and baseline as explanatory variables.

Sample size rationale

The original sample size of approximately 135 subjects in each treatment group was calculated using the following assumptions:

- Analysis of the primary efficacy criterion using Pearson's $\chi 2$ test at the $\alpha = 0.05$ significance threshold with a power $(1 - \beta) = 0.80$
- The percentage of subjects reducing their weekly rate of injection of the drug by at least 30% to be ≤ 10% in the active control (buprenorphine) group
- A minimal clinically relevant difference between groups of 15%.

Under these assumptions the required number of subjects was 226 (113 in each treatment group) to show a difference between treatments of at least 15%. Because a high rate of dropouts was anticipated in this population, 270 subjects were planned to be included. Due to slow recruitment, the study was terminated early after 158 subjects had been randomised (79 in each treatment group).

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SUMMARY & CONCLUSIONS

EFFICACY RESULTS:

Primary Efficacy Criterion

Reduction in Average Weekly Number of Study Drug Injections

The primary efficacy criterion was the percentage of subjects achieving a ≥ 30% reduction of the average weekly number of study drug injections during the post-baseline period (randomised treatment period [Day 1 to Day 84 inclusive]) as compared to the baseline period (pre randomisation period [Day -7 to Day -1]). Overall, 69.0% of subjects (87/126) in the ITT cohort, for whom injection data was available, achieved at least a 30% reduction in the average weekly number of study treatment injections; this reduction was achieved by 89.6% of subjects (60/67) in the buprenorphine/naloxone group compared with 45.8% of subjects (27/59) in the buprenorphine group. These results indicate that the combination of naloxone with buprenorphine substantially reduced the number of study drug injections compared with buprenorphine alone.

Secondary Efficacy Criteria

Average Number of Injections between Day 1 and Day 84

A secondary efficacy criterion was the mean number of injections of study treatment between Day 1 and Day 84. For the pre-randomisation period (Day -7 to Day -1), the mean number of injections was 19.47 in the buprenorphine/naloxone and 17.61 in the buprenorphine group. For the randomised treatment period (Day 1 to Day 84), the mean number of injections was substantially lower in the buprenorphine/naloxone group compared with the buprenorphine group (3.42 vs. 16.36) and compared with the pre-randomisation period, thereby supporting the primary endpoint finding.

For the buprenorphine/naloxone group, a substantial reduction from baseline in mean number of injections was observed during the first week of the treatment period (Day 1 to Day 7) when the mean number of injections was 5.22 and continued through to the final week of the treatment period (Day 78 to Day 84) when the mean number of injections had decreased further to 2.90. In contrast for the buprenorphine group, a marginal increase from baseline in mean number of injections was observed during the first week of the treatment period (Day 1 to Day 7) when the mean number of injections was 18.42, which fluctuated slightly in subsequent weeks through to the final week of the treatment period (Day 78 to Day 84) when the mean number of injections was 17.15. These results again support the primary endpoint finding.

Percentage of Subjects who Stopped Injecting the Study Drug

Another secondary efficacy criterion was the percentage of subjects who stopped injecting study treatment. For subjects with available injection data, 74.2% of subjects (49/66) in the buprenorphine/naloxone group stopped injecting the study drug compared with 15.9% of subjects (10/63) in the buprenorphine group. The percentage of subjects who never injected study drug was 47.4% of subjects (36/76) in the buprenorphine/naloxone group compared with 5.5% of subjects (4/73) in the buprenorphine group. These results support the primary endpoint finding.

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Severity of Opiate Withdrawal Symptoms on Days 28, 56 and 84

A further secondary efficacy criterion was to assess the severity of opiate withdrawal symptoms on Days 28, 56 and 84 using the OOWS and SOWS. At baseline, mean OOWS and SOWS scores indicated few opiate withdrawal symptoms in either treatment group. Some small changes in OOWS and SOWS scores were observed in both groups from baseline to Days 28, 56 and 84; however, no conclusions could be drawn given the high variance in data.

Severity of Addiction on Day 84

A further efficacy criterion was to assess the severity of addiction on Day 84 using the ASI. At baseline, all ASI treatment issues (medical, alcohol, drug, legal, family/social and psychological problems) were found to be of low severity, except for employment status, which was found to have a relatively high severity scoring in both treatment groups. Some small changes in ASI parameter scores were observed from baseline to end of study; however, no conclusions could be drawn given the high variance in data.

SAFETY RESULTS:

Overall, 57.4% of subjects in the Safety Set experienced an AE during the study; these occurred more frequently in the buprenorphine/naloxone group than in the buprenorphine group (63.9% of subjects vs. 51.3% of subjects). Most AEs were of mild or moderate intensity. Severe AEs accounted for 14.8% of all AEs and occurred to a similar extent in both treatment groups. Life-threatening AEs accounted for 1.6% of all AEs and occurred exclusively in the buprenorphine/naloxone group.

Individual severe or life-threatening AEs occurred in no more than 2 subjects in any treatment group; the most frequent were abscess (3 subjects), back pain and depression (each in 2 subjects). Abscess occurred in 2 subjects in the buprenorphine/naloxone group and 1 subject in the buprenorphine group; back pain occurred in 1 subject in each treatment group; and depression occurred exclusively in 2 subjects in the buprenorphine/naloxone group.

Treatment-related AEs accounted for 33.3% of all AEs and occurred to a greater extent in the buprenorphine/naloxone group than the buprenorphine group (38.4% vs. 27.4%). Individual treatment-related AEs occurred in no more than 3 subjects in either treatment group. The most frequent treatment-related AEs considered probably related to study treatment were withdrawal syndrome (4 subjects), abscess limb (2 subjects) and nightmare (2 subjects). Withdrawal syndrome occurred in 3 subjects in the buprenorphine/naloxone group and 1 subject in the buprenorphine group; abscess limb occurred exclusively in 2 subjects in the buprenorphine group; and nightmare occurred exclusively in 2 subjects in the buprenorphine/naloxone group. The most frequent AEs considered possibly related to study treatment were abdominal pain, abscess and anxiety (each in 3 subjects). Abdominal pain and abscess each occurred in 1 subject in the buprenorphine/naloxone group and 2 subjects in the buprenorphine group; while anxiety occurred in 2 subjects in the buprenorphine/naloxone group and 1 subject in the buprenorphine group.

No deaths occurred during this study. Serious adverse events accounted for 10.3% of all AEs and occurred to a similar extent in both treatment groups. Individual SAEs occurred infrequently in no more than 2 subjects in either treatment group; the most frequent were depression and abscess. Depression occurred in 1 subject in each group while abscess occurred exclusively in 2 subjects in the buprenorphine group.

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CONCLUSION:

The combination of naloxone and buprenorphine was substantially more effective than buprenorphine alone in reducing the intravenous misuse of buprenorphine in opioid-dependent subjects. This was evident from the high percentage of subjects achieving at least a ≥ 30% reduction in the average weekly number of buprenorphine injections in the buprenorphine/naloxone group compared with the buprenorphine group (89.6% vs. 45.8%) between the pre-randomisation period (Day -1 to Day -7) the treatment period (Day 1 to Day 84). These results were supported by the finding of substantially lower mean number of buprenorphine injections in the buprenorphine/naloxone group compared with the buprenorphine group (3.42 vs. 16.36) during the treatment period; as well as by the finding that a substantially greater percentage of subjects stopped injecting buprenorphine in the buprenorphine/naloxone group compared with the buprenorphine group (74.2% vs. 15.9%).

OOWS and SOWS results indicated no substantial changes in opiate withdrawal symptoms from baseline (at which few symptoms were observed) to Day 28, Day 56 and Day 84 in either treatment group.

ASI results indicated no substantial changes in severity of addiction scores from baseline (at which most parameters were of low severity) to the end of the study in either treatment group.

Safety findings indicated that the combination of naloxone with buprenorphine resulted in a slight overall increase in the number of AEs and treatment-related AEs compared with buprenorphine alone; however, most AEs were mild or moderate and severe AEs and SAEs occurred to a similarly low extent in both treatment groups.

Date of the report: 18 Sep 2013