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EVALUATION OF PREFERENCE FOR A BUPRENORPHINE-BASED MAINTENANCE THERAPY, AFTER A SWITCH FROM BUPRENORPHINE ALONE (SUBUTEX®) TO THE BUPRENORPHINE/NALOXONE COMBINATION (SUBOXONE®), IN OPIOID-DEPENDENT PATIENTS WITH BUPRENORPHINE MAINTENANCE THERAPY

CLINICAL STUDY REPORT - VOLUME 1/4

Other study Information:	This was a prospective multicenter, open-label study in adult opioid-dependent patients under stable buprenorphine 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg, 14 mg or 16 mg daily maintenance therapy. The study evaluated the patients' preference between buprenorphine hydrochloride only and buprenorphine hydrochloride / naloxone combination.
Name of Sponsor(s):	SCHERING-PLOUGH 92, rue Baudin, F-92 307 Levallois-Perret cedex
Included Protocol(s):	P05094
Development Phase of Study:	IV
Study Initiation Date:	11 July 2007
Study Completion Date:	21 December 2007
Sponsor's Responsible Medical Officer:	[redacted] SCHERING-PLOUGH, France Tel.: +33 (0) 141 06 35 00
Sponsor's Signature:	[redacted] ……
Sponsor's Contact Person:	[redacted]
GCP Compliance:	This study was performed in compliance with good clinical practice, including the archiving of essential documents.
Date of the Report:	Final version of 25 September 2008
Clinical Documentation Accession Number:	

2 SYNOPSIS

Title of the study: Evaluation of preference for a buprenorphine-based maintenance therapy, after a switch from buprenorphine alone (Subutex®) to the buprenorphine/naloxone combination (Suboxone®), in opioid-dependent patients with buprenorphine maintenance therapy

Scientific and medical coordinator:

[redacted]

CSST BIZIA, Centre Hospitalier de la Côte Basque, Bayonne, France.

Study centers: Ten centers located in France were opened and included at least one patient.

Publication(s): Not Applicable

Studied period:	**Clinical Phase:** IV
Initiation date: July 11, 2007 (first patient enrolled) Completion date: December 21, 2007 (last patient completed)	

Objectives:

Primary:. To evaluate the overall preference for a buprenorphine-based maintenance therapy after a switch from buprenorphine alone (Subutex®) to the buprenorphine/naloxone combination (Suboxone®) in opioid-dependent patients treated with Subutex® 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg, 14 mg, or 16 mg daily. The overall preference was to be evaluated from the patients' overall satisfaction level under each treatment, as assessed using visual analogic scales (VAS).

Secondary:

- To evaluate the preference of these patients for one of the two buprenorphine-based maintenance therapies in regards to: the tablet taste, the tablet size, the sublingual retention time, the well being over 24 hours, their wish to continue with Suboxone®.
- To compare both buprenorphine-based maintenance therapies in these patients in regards to, the sublingual retention time and the mode of tablet intake (together / successively).
- To further confirm the safety profile of Suboxone® in these patients.

Methodology:

Prospective, national (France), multicenter, open-label, comparative (Subutex® vs. Suboxone®), phase IV study performed in opiate-dependent patients under stable buprenorphine (2 mg to 16 mg daily) maintenance therapy.

The study consisted of six visits:

- Selection visit (Day -14 to -7): Written informed consent, checking of selection/exclusion criteria, selection of patients, baseline evaluations.
- Day 1: Checking of inclusion/exclusion criteria, inclusion of patients, start of study treatment (Subutex®), and evaluations during treatment.
- Day 2: Subutex®, evaluations during treatment.
- Day 3: Switch to Suboxone®, evaluations during treatment.
- Day 4: Suboxone®, evaluations during treatment.
- Day 5: Suboxone®, final evaluations, end-of-study visit.

Number of Patients:

- Planned: 52 patients were to be enrolled.
- Included: 60 patients. 52 patients completed the study.

Diagnosis and Criteria for Inclusion:

Patients treated for opioid dependence with Subutex® with a stable daily dose between 2 mg and 16 mg for at least 6 months, having given a written informed consent, ≥18 years of age, who did not inject / misuse their treatment with Subutex®, and free of illicit opiate drug use (urine test), could be included.

Patients with any disorder and/or medication that could interfere with the efficacy/safety assessments, or who did not respect the legal drug attachments were not to be included.

Test medication: Combination of buprenorphine hydrochloride / naloxone hydrochloride dehydrate (Suboxone®), tablets of 2 mg / 0.5 mg or 8 mg / 2 mg, sublingual route, batches #700501 and #702308, respectively.

Reference product: Buprenorphine hydrochloride (Subutex®), tablets of 2 mg or 8 mg, sublingual route, batches #7009 and #7025, respectively.

Criteria for evaluation:

The primary evaluation criterion was the Patient's overall preference for one of the two buprenorphine-based therapies, as assessed by the overall satisfaction under each treatment.

Efficacy measurements

- Patient's overall satisfaction towards the study drug, self-assessed using a 10-cm visual analogic scale (VAS) on each treatment day
- Patient's satisfaction in regards to the tablet taste, tablet size, sublingual retention time, and well-being over the past 24 hours, self-assessed using 10-cm VAS on each treatment day
- Patient's final preference for a formulation and wish to continue with Subuxone® (direct questioning on Day 5)
- Actual sublingual retention time of the tablet.

Safety measurements

Adverse events (AEs) reported from selection to Day 5, physical examination at selection and Day 5.

Statistical methods:

Populations for analysis:

Full analysis set (FAS): All patients selected in the study, i.e., having signed the informed consent.

Intent-to-treat (ITT) set: All evaluable patients included in the study, i.e., having signed the informed consent form and having taken one dose of Subutex® and one dose of Suboxone® at least. A total of 53 patients were included the ITT set.

Per protocol (PP) set: All evaluable patients included in the study and without any major protocol deviation at any time. A total of 45 patients were included in the PP set.

Demographic and other baseline characteristics, and compliance: ITT and PP sets

- Descriptive statistics.

Efficacy: ITT and PP sets ($\alpha = 0.05$).

- Overall preference (VAS, primary criterion): Descriptive statistics for the scores of overall satisfaction on Day 1 to Day 5. Analysis of covariance with repeated measurements (daily scores from Day 1 to Day 5), adjusted on treatment or treatment and dose.
- Preference in regards to the tablet taste, tablet size, sublingual retention time, and well-being over the past 24 hours (secondary criteria): Same analyses as for the primary criterion.
- Actual sublingual retention time (secondary criterion): Same analyses as for the primary criterion.
- Final preference for a treatment (secondary criterion): Descriptive statistics and 95% confidence intervals. One-sided test using the normal approximation to the binomial distribution to test whether the preferences on Day 5 were randomly distributed.
- Wish to continue with Suboxone® (secondary criterion): Descriptive statistics and 95% confidence intervals.

Safety: FAS and ITT sets

- Exposure to the study drug: Descriptive statistics.
- Adverse events (AEs): Descriptive statistics.
- Physical examination: Descriptive statistics.
- Concomitant treatments: Descriptive statistics.

SUMMARY - CONCLUSIONS

PATIENTS

Ten study centers selected 60 patients and included a total of 53 patients treated for opiate dependence with Subutex® (2 mg to 16 mg daily). A total of 7 patients were withdrawn prematurely from the study (6 before taking one dose of study treatment and 1 on Day 3 postdose) and one patient was lost to follow-up before the inclusion visit. Overall, 53 patients were included in the ITT analysis set and 52 completed the end-of-study visit (Day 5). One patient did not perform the Day 2 visit and assessments and 6 patients did not perform the Day 3 assessments. For the ITT analysis, the corresponding missing data were replaced by the Day 1 data for the first patient, and by the mean of the Day 4 and Day 5 data for the other 6 patients. The PP analysis was carried out in the 45 patients without protocol deviation. The safety analyses were performed in all the 53 included patients (ITT set).

EFFICACY RESULTS

Baseline characteristics

The ITT set included 38 (72%) men and 15 (28%) women aged 38.9 ± 8.6 years (range 21 – 56). Most patients (96%) were in a stable housing situation and had an employment pay (51%). The patient's health was considered as good or very good for all patients except one who had dysuria. As expected in patients with maintenance therapy, the most frequent histories recorded were psychiatric disorders (mainly depression, anxiety and psychotic disorders), infections (HCV) and nervous system disorders (mainly sleep disorders). However at selection, no patient had a clinically significant disorder which, in the opinion of the investigator, may interfere with the study evaluations.

Most patients reported having taken heroin (94%) and cocaine (93%) and/or other opiates during their life, 74% were intravenous drug users. The first consumption occurred at the mean age of 20.4 ± 4.4, that are 18.5 ± 8.4 years before the study was carried out. At selection, most of patients 60% reported having taken psychoactive drugs, alcohol (72%), and tobacco (96%) within the past month. At inclusion, 13 (25%) patients reported having taken psychoactive drugs (mainly cannabis) since the selection visit.

Patients in the ITT set were first prescribed Subutex® on average 7.30 ± 3.65 years prior to selection. At the selection visit, the most frequent current daily doses were 8 mg in 16 (30%) patients, 6 mg in 10 (19%) patients, and 16 mg in 9 (17%) patients.

Compliance to treatment. In the ITT set, one patient did not receive the Day 2 Subutex® dose in the presence of the investigator, 6 patients did not receive Suboxone® on Day 3, and 1 patient was withdrawn from the study on Day 3. Hence, compliance to treatment was good (2 days of Subutex® and 3 days of Suboxone®) for 45/53 (85%) patients. However, treatment duration was 5 days for 52 (98%) patients. The daily dose of buprenorphine remained unchanged in all patients during the study.

Validation of the assessments. Before and during treatment with the study drug, no event occurred that may have interfered with the assessments. The population was heterogeneous in terms of consumptions between Day 1 and Day 5 (meals/beverages, psychoactive drugs).

Evaluations

- **Overall preference (primary criterion)** - The main result of this study is that overall satisfaction of the patients towards the study drug, as self-assessed using a 10-cm VAS, was similar with Subutex® and Suboxone® (p=0.130, ITT set). Hence, there was no overall preference for Subutex® or Suboxone®.

  There was no significant impact of the doses on the degree of overall satisfaction.

- **Preference in regards to the tablet taste, size, and sublingual retention time** – Unlike the overall satisfaction of the patient, a preference in regards to intrinsic characteristics of the tablet was demonstrated. There was a significant impact of the treatment on satisfaction in regards to its taste (p<0.001), size (p=0.001), and sublingual retention time (p<0.001, ITT set), as self-assessed using a VAS, with large differences between products (as estimated by the Ancova test) in favor Suboxone®: 4.3, 1.1, and 2.8 points, respectively. Hence, Suboxone® was preferred over Subutex® in regards to the intrinsic characteristics of the tablets.

  There was no significant impact of the doses on the degree of satisfaction in regards to these three criteria.

- **Preference in regards to the well being over 24 hours** – Satisfaction of the patients in regards to the well being over 24 hours, as self-assessed using a VAS, was similar with Subutex® and Suboxone® (p=0.144, ITT set). Hence, there was no preference for Subutex® or Suboxone® in this respect.

  There was no significant impact of the doses on the degree of satisfaction in regards to the well being.

- **Final preference for a treatment (Day 5 postdose, post-VAS)** - The results of the daily self-evaluations were confirmed by direct questioning after the last study drug intake. Indeed, 54% of the patients answered preferring Suboxone® and 15% answered having no preference for one of the two treatments. Furthermore, 71% wished to continue with Suboxone® if it were available.

- **Actual sublingual retention time** – The results could not be interpreted as the sample size in each category (per dose and per mode of intake) was too small.

No significant impact of the treatment doses was observed, whatever the efficacy criterion and the set analyzed. All the results obtained in the ITT analyses were confirmed by those in the PP analyses. Also, there was no significant global time effect whatever the criterion and the set analyzed. This suggests that the study duration was sufficient to obtain stable data over time.

SAFETY RESULTS

Analysis of adverse events raised no safety concerns.

No death, other serious adverse events, or other significant TEAE occurred during this study (one patient died before any study drug intake). Overall, 14 (26%) patients in the ITT set experienced a total of 26 AEs during the study, of which 23 were treatment emergent: 5 TEAEs in 4 (8%) patients started between Day 1 postdose and Day 3 predose (under Subutex®) and 18 TEAEs in 8 (15%) patients started after Day 3 postdose (under Suboxone®).

Of the 23 TEAEs, 19 were considered as treatment-related by the investigator: 2 TRTEAEs in 2 (4%) patients started between Day 1 postdose and Day 3 predose (under Subutex®) and 17 TRTEAEs in 10 (19%) patients started after Day 3 postdose (under Suboxone®).

Irrespective of the buprenorphine-based treatment, no TEAE occurred that was unexpected in regards to the known safety profile of both treatments as well as in regards to the population studied, with frequent psychiatric background.

The fact that most TEAEs started after the first intake of Suboxone® was expected. Patients were taking Subutex® since several months, whereas they took Suboxone® for the first time in this study. As in any open study involving a new treatment, patients and physicians paid great attention to any untoward sign or symptom that could have occurred after its administration. This is particularly true in psychologically fragile populations such as our study population, and especially in case of switch from a well-known treatment to a new treatment.

For these reasons, it is reasonable to conclude that both Subutex® and Suboxone® were well tolerated.

CONCLUSION

In conclusion, analysis of the daily assessments clearly showed that the overall satisfaction of patients with buprenorphine maintenance therapy was similar with both buprenorphine-based treatments, as was their well being over 24 hours. The buprenorphine/naloxone combination (Suboxone®) was preferred when considering the intrinsic tablet characteristics (tablet taste, tablet size, sublingual retention time) only. Answers to the final Day 5 direct questioning were consistent with these daily assessments. In particular, over two thirds of patients wished to continue the treatment with Suboxone®, if it were available. Administration of Suboxone® raised no safety concerns.

Date of the report: Final version of 25 September 2008.