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A RANDOMIZED ACCEPTABILITY AND SAFETY STUDY OF THE TRANSFER FROM SUBUTEX® (SCH 28444 BUPRENORPHINE) TO SUBOXONE® (SCH 484 BUPRENORPHINE/NALOXONE) IN OPIOID-DEPENDENT SUBJECTS

Other Study Information: This was a prospective, randomized, multicenter parallel-group study (1-week double-blind, double-dummy phase followed by 3-week open-label phase) comparing sublingual once-daily treatment of 4 mg/1.0 mg to 24 mg/6.0 mg buprenorphine/naloxone vs 4 to 24 mg buprenorphine.

Name of Sponsor(s): Schering-Plough Research Institute, a division of Schering Corporation

Included Protocol(s): P04843

Development Phase of Study: 4

Study Initiation Date: 04 MAR 2008

Study Completion Date: 28 MAY 2009

Sponsor's Responsible Medical Officer: [redacted]
Group Vice President
Global Medical Affairs

Sponsor's Signatory:

[redacted]
Global Medical Director
CNS-Neuroscience
Global Medical Affairs

Sponsor's Contact Person:

[redacted]
Senior Regulatory Affairs Scientist
Global Regulatory Affairs
Schering-Plough Europe
Oss, Netherlands 5340BH
Telephone: +31-412-663417
FAX: +31-412-662571

GCP Compliance:

This study was performed in compliance with good clinical practice, including the archiving of essential documents.

Date of the Report:

27 MAY 2010
(replaces 04 DEC 2009)

Doc ID:

5126681

2 SYNOPSIS

Title of Study:	A RANDOMIZED ACCEPTABILITY AND SAFETY STUDY OF THE TRANSFER FROM SUBUTEX® (SCH 28444 BUPRENORPHINE) TO SUBOXONE® (SCH 484 BUPRENORPHINE/NALOXONE) IN OPIOID-DEPENDENT SUBJECTS (PROTOCOL NO. P04843)
Investigator(s): Multicenter	
Study Center(s): Multicenter: 26 centers in 10 European countries: Croatia (3), Denmark (1), France (8), Italy (4), Lithuania (2), Norway (1), Portugal (2), Slovenia (2), Sweden (2), and the United Kingdom (1).	
Publication(s): None	
Studied Period: 04 MAR 2008 to 28 MAY 2009	**Clinical Phase:** 4
Objective(s): The primary objective of this study was to demonstrate that Suboxone was not inferior to Subutex as measured by response rate by the Day 7 Visit. The response rate was assessed by determining the proportion of subjects in each group who did not receive a dose increase during the double-blind, double-dummy phase. Secondary objectives included assessments of illicit opioid and nonopioid use, withdrawal symptoms, compliance rate, treatment retention, time to dose increase, and frequency and severity of adverse events.	
Methodology: This was a prospective, randomized, multicenter parallel-group study (a 1-week double-blind, double-dummy phase followed by a 3-week open-label phase) comparing sublingual once-daily treatment of 4 mg/1.0 mg to 24 mg/6 mg of buprenorphine/naloxone vs 4 to 24 mg of buprenorphine alone. A follow-up assessment took place at Week 8.	
Number of Subjects: A total of 251 subjects were screened for inclusion in this trial, 10 of whom were screen failures. The remaining 241 subjects were randomly assigned in a 2:3 ratio to continue receiving Subutex (n = 98) or to receive Suboxone (n = 143). One subject in the Subutex group was subsequently withdrawn before receiving study medication and was not included in the intent-to-treat (ITT) analysis. Subject demographics were well matched; most subjects in the ITT population were men (Suboxone 79%, Subutex 77%), approximately 36 years of age (Suboxone 35.8 ± 8.2 years; Subutex 35.5 ± 8.7 years), and receiving an average pre-randomization Subutex daily dose of 10 mg (Suboxone arm 10.4 ± 5.0 mg; Subutex arm 9.8 ± 5.0 mg).	
Diagnosis and Criteria for Inclusion: Subjects had to meet the criteria for opioid dependence as defined in the *Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision* (DSM-IV-TR), have been receiving maintenance treatment with Subutex at daily doses ranging from 4 to 24 mg for at least 1 month prior to Screening, and have reported not injecting opioids more than 4 times in the past 30 days prior to Screening.	
Test Product, Dose, Mode of Administration, Batch Nos: SCH 484-Suboxone tablets, each containing 2 mg of buprenorphine/0.5 mg naloxone, or 8 mg of buprenorphine/2 mg naloxone; administered sublingually once-daily at a dose range of 4 mg/1 mg to a maximum dose allowed by country labeling requirements, but not to exceed 24 mg/6 mg per day. Dosage was subject dependent. Manufacturer Lot Nos. of Suboxone active drug used in the trial were 707509 and 724203 (417498 and 418845 were for Suboxone placebo).	
Duration of Treatment: Duration of treatment included a screening phase of up to 1 week with continued use of Subutex (4 up to 24 mg per day); a 1-week double-blind, double-dummy treatment transfer phase; a 3-week open-label treatment phase; and a follow-up assessment at Week 8.	
Reference Therapy, Dose, Mode of Administration, Batch Nos: SCH 28444-Subutex tablets, each containing 2 or 8 mg of buprenorphine administered sublingually once daily at a dose range of 4 mg to a maximum dose allowed by country labeling requirements, but not to exceed 24 mg/day. Dosage was subject dependent. Manufacturer Lot Nos. of Subutex active drug used in the trial were 719306, 720805, 800404, 801704, 814305, and 815404 (381641 and 397280 were for Subutex placebo).	
Criteria for Evaluation: The primary efficacy variable was the proportion of responders (response rate) by the Day 7 Visit, where responders were subjects who did not receive a dose increase during the 1-week double-blind, double-dummy transfer phase.	
Statistical Methods: The response rates for the two treatment groups were calculated. The two-sided 95% confidence interval (CI) for the difference in the response rate (Suboxone minus Subutex) was calculated. Non-inferiority was claimed if the lower bound of the two-sided CI was greater than -0.15. The primary efficacy analysis was based on the ITT population. Analysis using the per-protocol (PP) population was used to support	

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the ITT primary efficacy results.

Urine drug screening (UDS) results were analyzed using methods similar to those for the primary analysis. Change from Baseline in the Addiction Severity Index (ASI)-Lite was analyzed using the analysis of covariance (ANCOVA) model including treatment as the fixed effect and Baseline as the covariate. Substance Use Inventory (SUI) and Subjective Opiate Withdrawal Scale (SOWS) were each analyzed using a repeated measures mixed model including the fixed effects of treatment and visit, and the treatment-by-visit interaction. Compliance rate, treatment retention, and time to dose increase were summarized by treatment group.

Categorical variables were summarized by frequency and percentage; continuous variables were summarized by N, mean, median, standard deviation, and range.

SUMMARY-CONCLUSIONS:

RESULTS:

Efficacy: The proportion of subjects who did not receive dose increases during the transfer period (ie, primary objective) were 83.2% (119/143) in the Suboxone group and 88.7% (86/97) in the Subutex group (absolute difference, 5.4%; 95% CI, − 14.2, 3.4). These results fulfilled the non-inferiority criterion for Suboxone. The maximum dose increase during the transfer period was 3.7 mg in the Suboxone group and 2.9 mg in the Subutex group; the primary reason for the dose increase was increased incidence of withdrawal-related adverse events (AEs). Compliance and retention rates across treatment groups were excellent, averaging 99% and 96% for Suboxone and Subutex, respectively, with no statistically significant differences between groups. There were also no significant differences between the groups in illicit drug use, change from Baseline in withdrawal scores, change from Baseline in ASI-Lite composite scores, or time to dose increase. There were no reports of intravenous misuse of Suboxone during the entire study, despite weekly access to take-home therapy beginning at Week 2.

Overall, the majority of subjects (232/240, or 97%) reported continuing with agonist substitution treatment at follow-up. In France and Croatia (where Suboxone was not yet available at the time of follow-up) nearly all subjects continued treatment with Subutex (98% vs 95% for the Suboxone and Subutex groups, respectively). In the remaining countries where Suboxone was readily available, 66% of Suboxone subjects continued with Suboxone treatment, with the majority of the other Suboxone subjects returning to Subutex at follow-up; and 18% of Subutex subjects switched to Suboxone, with the majority of the other Subutex subjects remaining on Subutex at follow-up.

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Safety: Overall, 66% (158/240 subjects) had at least 1 treatment-emergent adverse event (TEAE) during the trial. A total of 58% (139/240 subjects) had an event in the 1-week Transfer Phase and 37% (87/234 subjects) in the 3-week Open-Label Phase.

The overall incidence of TEAEs was similar for both groups (Suboxone, 67%; Subutex, 64%), as was the incidence of TEAEs leading to study discontinuation (Suboxone, 1%; Subutex, 2%). The most common TEAEs reported by subjects were similar across the treatment groups. The most common TEAEs in subjects receiving Suboxone were anxiety (16%), headache (16%), and nausea (15%); the most common TEAEs in subjects receiving Subutex were anxiety (16%), headache (12%), and insomnia (10%).

While the overall incidence of treatment-related TEAEs was higher in subjects receiving Suboxone (48%) than in subjects receiving Subutex (37%), during the double-blinded phase of the study the rates of treatment-related TEAEs were more comparable (38% vs 32% for Suboxone and Subutex groups, respectively). Of the overall safety population, 105 treated subjects (44%) reported at least 1 TEAE during the study that was considered by the investigator to be possibly or probably related to study medication. Hyperhidrosis and anxiety were the most frequently occurring treatment-related TEAEs in the overall safety population: each treatment-related TEAE had incidences of 10% in the Suboxone group and 8% in the Subutex group. Only 8 of 240 subjects overall (3%) had a TEAE classified as severe.

There were no deaths in this trial, and only 6 subjects sustained a serious adverse event (SAE: 2 Suboxone, 4 Subutex subjects). Most SAEs (in 4 of 6 subjects) occurred during the follow-up period. All SAEs were considered by the investigator to be unlikely related to study drug, and all SAEs subsequently resolved.

Of the 241 randomized subjects in this study, 190 subjects used a total of 214 concomitant medications during the trial: 78% of Suboxone subjects and 81% of Subutex subjects.

No laboratory results were analyzed in this trial.

CONCLUSIONS*:*

The following conclusions can be drawn from this study:

- Most patients can be acceptably and safely transferred from Subutex to Suboxone without the need for a dose increase.
- A minority of subjects in both groups did require a post-switch dose increase on the order of 30%, primarily because of withdrawal-related TEAEs.
- There were no differences across the groups in a range of secondary endpoints; notably, treatment retention and compliance were excellent in both groups.
- The incidence and type of TEAEs were similar in both groups.
- There were no reports of intravenous misuse of Suboxone throughout the study despite weekly access to take-home therapy as of Week 2.
- The overall efficacy and safety findings illustrate that in the group of stable Subutex-maintained subjects who entered the study, no subject was destabilized by the switch from Subutex to Suboxone.
- Suboxone was shown to be an appropriate alternative to Subutex that allows patients to continue their maintenance regimen with a reduced risk for intravenous misuse, which could potentially also reduce drug diversion.

Date of the Report: 27 MAY 2010 (replaces 04 DEC 2009)