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A RANDOMIZED ACCEPTABILITY AND SAFETY STUDY OF SUBOXONE® (SCH 484 BUPRENORPHINE/NALOXONE) INDUCTION IN HEROIN USERS

Other Study Information: This was a prospective, randomized, multi-center, parallel-group study of Direct Suboxone Induction versus Subutex® [SCH 28444 buprenorphine]-to-Suboxone Induction in the maintenance treatment of opioid dependence. In the double-blind, double-dummy phase (2 days), subjects received fixed doses (8 mg Day 1; 16 mg Day 2) of either Suboxone or Subutex. In the Suboxone Open-Label phase, all subjects received 16 mg Suboxone on Day 3, followed by flexible doses of Suboxone ranging from 8 mg to 24 mg/day through Day 28 with weekly access to take-home therapy.

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

Included Protocol: P05042

Development Phase of Study: 4

Study Initiation Date: 11 MAR 2008

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Study Completion Date: 11 DEC 2009

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GCP Compliance:	This study was performed in compliance with good clinical practice (GCP), including the archiving of essential documents.
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2 SYNOPSIS

Title of Study:	A RANDOMIZED ACCEPTABILITY AND SAFETY STUDY OF SUBOXONE® (SCH 484 BUPRENORPHINE/NALOXONE) INDUCTION IN HEROIN USERS (Protocol No. P05042)
Investigators: Multicenter	
Study Centers: Multicenter: 19 centers in 10 European countries: Czech Republic (2 centers), Croatia (1), France (3), Ireland (1), Italy (2), Lithuania (2), Portugal (2), Slovenia (1), Spain (3), United Kingdom (2)	
Publications: None	
Studied Period: 11 MAR 2008 to 11 DEC 2009	**Clinical Phase:** 4

Objectives:

The primary objective was to demonstrate that Direct Suboxone Induction is not inferior to Subutex-to-Suboxone Induction, as measured by response rate at Day 3. Response rate was assessed by determining the proportion of subjects in each group who received the scheduled dose of Suboxone at the Day 3 study visit.

The secondary objectives of this study assessed the overall clinical response to Suboxone as a function of the induction strategy by comparing the response of subjects induced directly with Suboxone with the response of those induced with a Subutex-to-Suboxone procedure, using the following measures:

1) Illicit opioid and non-opioid drug use as measured by urine drug screening (UDS);

2) Illicit opioid and non-opioid drug use as measured by self-report on the Substance Use Inventory (SUI);

3) Self-reported opioid withdrawal symptoms as measured by the Subjective Opiate Withdrawal Scale (SOWS);

4) Observer-rated opioid withdrawal symptoms as measured by the Objective Opiate Withdrawal Scale (OOWS);

5) Addiction-related problem profiles as measured by the Addiction-Severity Index (ASI)-Lite;

6) Compliance rate;

7) Response rate (ie, the proportion of subjects in each group who received the scheduled doses of Suboxone by visit (Visits 5 to 9).

The frequency and severity of adverse events (AEs) and use of concomitant medications were also assessed.

Methodology*:*

This was a prospective, randomized, multicenter parallel-group study comparing sublingual once-daily treatment of Direct Suboxone Induction vs Subutex-to-Suboxone Induction. There was a 2-day double-blind, double-dummy fixed-dose period, during which subjects received a sublingual bolus dose of 8 mg of Suboxone or 8 mg of Subutex on Day 1, and a sublingual bolus dose of 16 mg of Suboxone or 16 mg of Subutex on Day 2. On Day 3, all subjects received an open-label bolus dose of 16 mg of Suboxone; thereafter all subjects received flexible sublingual bolus daily doses of 8 mg to 24 mg of Suboxone in an open-label manner through Day 28 with weekly access to take-home therapy.

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

Number of Subjects: A total of 188 subjects were randomly assigned in a 1:1 ratio to the Direct Suboxone Induction group or to the Subutex-to-Suboxone Induction group. One subject from the Subutex-to-Suboxone Induction group was subsequently withdrawn before receiving study medication and was not included in the intent-to-treat (ITT) population nor in the safety population. The ITT population included 46 women (25%) and 141 men (75%). Almost all subjects in the study were white (95%). Mean age (standard deviation, SD) for all ITT subjects was 30.7 years (SD = 8.3 years), and median age overall and within treatment groups was 29.0 years (overall range 17 to 53 years). Of the 187 subjects who received treatment, 136 subjects (73% completers) were still in the study at Day 28.

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, Fourth Edition, Text Revision (DSM-IV-TR)*. All subjects had to have a methadone- and buprenorphine-negative UDS result before randomization. Subjects could not have methadone or buprenorphine maintenance or detoxification within 30 days of enrollment.

Test Product, Dose, Mode of Administration, Batch No(s): SCH 484—Suboxone tablets each contained 2 mg of buprenorphine/0.5 mg of naloxone, or 8 mg of buprenorphine/2 mg of naloxone, and were administered sublingually on Days 1 and 2 to subjects in the Direct Suboxone Induction group. Dosage of Suboxone was 8 mg once daily on Day 1 (administered as a single 8-mg tablet), and 16 mg (administered as two 8-mg tablets) once daily on Day 2. On Day 3, all subjects in the study received sublingual Suboxone, administered as two

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8-mg tablets. On Days 4 to 28, dosage for all subjects in the study ranged from a minimum of 8 mg/day to a maximum of 24 mg/day and was titrated according to subject need using 2-mg or 8-mg tablets; no tablets were broken. Manufacturer Lot Nos. of Suboxone active drug were 724203 (2 mg) and 702502 (8 mg). The Lot No. for Suboxone placebo was 417498 (8 mg).

Duration of Treatment: After a screening period of up to 1 week, subjects were enrolled and randomized 1:1 to a 2-day double-blind, double-dummy fixed-dose period during which subjects received either 8 mg of Suboxone or Subutex on Day 1, followed by 16 mg of Suboxone or Subutex on Day 2. On Day 3, all subjects regardless of randomized treatment group assignment received 16 mg of Suboxone in an open-label manner, followed by flexible-dose Suboxone treatment on Days 4 through 28 within the range of 8 mg/day to 24 mg/day. Upon completion of the study, subjects were allowed to continue appropriate treatment as clinically indicated and available in each participating country.

Reference Therapy, Dose, Mode of Administration, Batch No(s): SCH 28444—Subutex tablets each contained 8 mg of buprenorphine, and were administered sublingually. Dosage of Subutex was 8 mg once daily (administered as a single 8-mg tablet) on Day 1, and 16 mg (administered as two 8-mg tablets) once daily on Day 2. Manufacturer Lot Nos. of Subutex active drug were 719306 (8 mg), 800404 (8 mg), 814305 (8 mg), 827508 (8 mg), and 902903 (8 mg). The Lot No. for Subutex placebo was 381641 (8 mg).

Criteria for Evaluation*:* The primary efficacy variable was the proportion of responders (response rate), where responders were defined as subjects who received the scheduled dose of 16 mg of Suboxone at the Day 3 study visit.

Statistical Methods: The primary efficacy variable was the response rate to treatment assignment, assessed by determining the proportion of subjects in each group who received the scheduled 16-mg dose of Suboxone at the Day 3 study visit. The response rates for the two treatment groups were calculated along with the two-sided 95% confidence interval (CI) for the difference in the response rate (Direct Suboxone Induction minus Subutex-to-Suboxone Induction). Non-inferiority was claimed if the lower bound of the two-sided 95% CI was greater than -10%. The primary efficacy analysis was based on the ITT population. Analysis using the per-protocol (PP) population was used to explore further the ITT primary efficacy results.

UDS and SUI results were analyzed using methods similar to those for the primary analysis. Change from Baseline in the ASI-Lite was analyzed using an analysis of variance (ANOVA) model including treatment as the fixed effect. SOWS and OOWS were each analyzed using a repeated measures mixed model that included the fixed effects of treatment and visit, and the treatment-by-visit interaction. Compliance rate was analyzed using a t-test. Treatment retention was analyzed using a log-rank test and a t-test.

Response rate (defined as the proportion of subjects in each group who received the scheduled doses of Suboxone by visit [Visits 5 to 9]) was analyzed using methods similar to those for the primary analysis.

Categorical variables were summarized by frequency and percentage; continuous variables were summarized by N, mean, median, standard deviation, and range. The extent and type of concomitant medications used were summarized descriptively.

Missing values for the primary efficacy variable were treated as failures. No interim analysis was planned or performed.

SUMMARY-CONCLUSIONS:

RESULTS:

Efficacy*:* Direct Suboxone Induction proved to be non-inferior to Subutex-to-Suboxone Induction, as measured by the proportion of subjects in each treatment group who received the scheduled dose of 16 mg of Suboxone at the Day 3 study visit: 91.4% (85/93) Direct Suboxone Induction vs 90.4% (85/94) Subutex-to-Suboxone Induction (difference, 1.0%; 95%CI, -7.3%, 9.2%). Compliance across treatment groups was excellent, averaging 98.7% for Direct Suboxone Induction vs 98.4% for Subutex-to-Suboxone Induction, with no statistically significant differences between groups ($p = 0.697$). Median retention rates were 96% for both groups. The average daily dose of Suboxone during the Open-Label phase was 15.3 mg and was identical across groups. There were also no significant differences between the groups in terms of illicit drug use as measured by UDS, change from Baseline in withdrawal scores as measured by both SOWS ($p = 0.868$) and OOWS ($p = 0.912$), and change from Baseline in ASI-Lite scores (except for employment satisfaction). There were no reports of intravenous misuse of Suboxone during the entire study, despite weekly access to take-home therapy beginning at Day 4.

Safety: The Overall incidence of treatment-emergent AEs (TEAEs) was similar for both groups (Direct Suboxone Induction, 75%; Subutex-to-Suboxone Induction, 74%). The most common TEAEs Overall in subjects receiving Direct Suboxone Induction vs Subutex-to-Suboxone Induction were insomnia (27% vs 28%),

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hyperhidrosis (24% vs 22%), and anxiety (20% vs 17%), respectively.

The incidence of treatment-related TEAEs was an identical 51% in both groups. The most common treatment-related TEAEs Overall were hyperhidrosis (12% vs 16%), insomnia (11% vs 10%), vomiting (11% vs 10%), and drug dependence (11% vs 5%) for Direct Suboxone Induction vs Subutex-to-Suboxone Induction, respectively.

There were no deaths in this study. Five subjects in each treatment group had a severe (4 subjects) or life-threatening (1 subject, rash) treatment-related TEAE considered possibly or probably related to study drug by the investigator.

Four subjects had a total of 6 serious adverse events (SAEs): 1 subject in the Direct Suboxone Induction group had a total of 3 SAEs (depression, drug dependence, personality disorder), and 3 subjects in the Subutex-to-Suboxone Induction group each had 1 SAE (abscess limb, epilepsy, and rash). Except for the rash (life-threatening, probably related to study drug, and for which the subject discontinued study medication), all SAEs involved hospitalization and were considered unlikely related to study medication per the investigator.

Five subjects (1 subject in the Direct Suboxone Induction phase, 4 subjects in the Subutex-to-Suboxone Induction phase) with a total of 6 TEAEs discontinued from the study due to adverse events. Of the 5 subjects, 3 subjects had a total of 4 TEAEs in the Double-Blind Period (anxiety, feeling cold, hot flush, vomiting), and 2 of the 5 subjects had SAEs (abscess limb, life-threatening rash) in the Open-label period. The investigator considered the case of vomiting as possibly related to study drug, and feeling cold, hot flush, and rash as probably related to study drug.

CONCLUSIONS*:*

The following conclusions can be drawn from this study:

- Most patients can be acceptably and safely induced directly with Suboxone without the need for an initial bridging strategy using Subutex over the first few days of treatment.
- An initial once-daily bolus dose of sublingual 8 mg of Suboxone followed by a bolus dose of 16 mg of Suboxone on Day 2 is safe and effective.
- An average Suboxone maintenance dose of 15.3 mg across treatment groups produced high rates of treatment compliance and retention, and illicit opioid abstinence.
- There were no differences across treatment groups in a range of secondary endpoints; notably, overall clinical response was excellent in both groups.
- The incidence and type of TEAEs were similar in both treatment groups.
- There were no reports of intravenous misuse of Suboxone throughout the study despite weekly access to take-home therapy beginning at Day 4.
- Direct Suboxone Induction is an acceptable and safe induction strategy that allows patients to be treated for opioid dependence with a single medication while maintaining a reduced risk for intravenous misuse, which could potentially also reduce drug diversion.

Date of the Report: 23 JUN 2010