This report may include approved and non-approved uses, formulations, or treatment regimens. The results reported may not reflect the overall profile of a product. Before prescribing any product mentioned in this report, healthcare professionals should consult local prescribing information for the product approved in their country.

2.0 SYNOPSIS

Title of Study: A PROSPECTIVE, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL INVESTIGATING THE EFFICACY AND SAFETY OF SCH 900435 (Org 25935) IN RELAPSE PREVENTION IN SUBJECTS WITH ALCOHOL DEPENDENCE (Protocol No. P05718, formerly 172009)		
Proprietary Drug Name: NA	**Generic Drug Name:** SCH 900435	**Therapeutic area and FDA-approved indications:** Glycine uptake inhibitor for alcohol-dependence
Name of Sponsor/Company: Schering-Plough Research Institute, a division of Schering Corporation.		
Investigators: Multicenter.		
Study Centers: Multicenter: Subjects were recruited in 18 centers in Australia, Belgium, Finland, Germany, Norway and Sweden. In addition, two sites in Italy and one site in the Netherlands were approved to participate but did not enroll any subjects.		
Publication: None.		
Studied Period: 16 APR 2009 (first visit) to 11 AUG 2010 (last contact)		Clinical Phase: 2A

Objective(s):

Primary objective:

- To assess the effects of SCH 900435 (Org 25935) on heavy drinking in subjects with alcohol dependence.

Secondary objectives:

- To assess the effects of SCH 900435 on the amount of drinking.
- To assess the effects of SCH 900435 on the first relapse to heavy drinking
- To assess the effects of SCH 900435 on abstinence.
- To assess the safety and tolerability of SCH 900435.
- To explore potential predictors of response to SCH 900435.

Methodology:

This was a multi-site, randomized, double-blind, two-arm, placebo-controlled, parallel-group trial assessing the efficacy and safety of 12 mg SCH 900435 twice daily (BID) versus placebo in relapse prevention in subjects with alcohol dependence who recently completed an alcohol detoxification program.

Subjects were randomly assigned to receive 12 mg SCH 900435 BID or placebo in a 1:1 ratio for a total of 12 weeks.

This study was performed in compliance with good clinical practice.

Number of Subjects:

A total of 300 subjects was planned to be recruited, 150 in each treatment group.

Subject enrollment was interrupted in January 2010, and an interim analysis was performed when all recruited subjects had completed the last study visit and data validation had been finalized. Based upon the outcome of the interim analysis, the study was stopped early due to futility on 25 June 2010. In total, 175 subjects were screened for trial eligibility; 141 were treated (75 SCH 900435 and 66 placebo) and 108 completed the treatment phase (53 on SCH 900435 and 55 on placebo).

Diagnosis and Criteria for Inclusion:

Inclusion criteria:

1. Provide written informed consent after the scope and nature of the investigation have been explained to the subject before screening;
2. Diagnosis of alcohol dependence - meeting at least 5 out of 7 criteria according to diagnostic and statistical

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manual of mental disorders edition IV text revision (DSM-IV-TR) specifier, one of which should be criterion 1 (tolerance) or 2 (withdrawal);

3. Primary complaints according to Mini-International Neuropsychiatric Interview (MINI) should be alcohol problems;
4. Subjects must have gone through a detoxification program, have a clearly stated desire to stay abstinent and present at baseline with the following: be alcohol abstinent for at least 3 days, benzodiazepine free for at least 3 days, and a Clinical Institute Withdrawal Assessment (CIWA) score < 10;
5. Age 18-65 years at screening;
6. Males, or females who are not of childbearing potential (ie., surgically sterile, postmenopausal for at least 1 year) or who are non-pregnant, non-lactating and using a medically accepted method of contraception; these include condoms with or without a spermicidal agent, diaphragm or cervical cap with spermicide, medically prescribed intra uterine device (IUD), and hormonal contraceptives;
7. BMI > 16 kg/m^2;
8. Breath alcohol concentration < 0.02% (at screening and at baseline).

Exclusion criteria:

1. Subjects requiring pharmacological treatment for a primary diagnosis of major depressive disorder, anxiety, panic disorder or social phobia;
2. Subjects with psychotic disorders (according to MINI);
3. Subjects with a medium or high suicidality risk (as assessed by MINI);
4. Active substance abuse (resulting in either physical or mental damage as defined by ICD10) or dependence other than alcohol (excluding nicotine) within 12 months prior to screening, e.g. cannabis, benzodiazepine, amphetamines, chlo(r)methiazole, opiates, cocaine, hallucinogens or other substances;
5. Use of one of the following drugs during the last 14 days prior to screening: cannabis, amphetamines, opiates, cocaine, hallucinogens;
6. Use of any medication that can have an effect on alcohol consumption within 30 days of study initiation, including naltrexone, acamprosate, disulfiram, ondansetron, topiramate, selective serotonin reuptake inhibitors, mirtazapine, varencicline, gabapentin, levetiracetam;
7. A clinically relevant visual disturbance, such as cataract, color blindness, macular degeneration, glaucoma or retinal disease;
8. Untreated or uncompensated clinically significant renal, endocrine, hepatic, respiratory, cardiovascular, hematological, immunological or cerebrovascular disease, malignancy, or other chronic and/or degenerative process at screening;
9. Any clinically meaningful abnormal laboratory, vital sign, physical examination or electrocardiogram (ECG) finding which, in the opinion of the investigator, may interfere with the interpretation of safety or efficacy evaluations;
10. QTc interval (Frederica corrected) at screening >450 ms (male), >470 ms (female);
11. Serious neuropsychiatric condition that can impair judgment or cognitive function (including dementia or amnestic disorder) to an extent that providing informed consent or complying with treatment is precluded;
12. History or present evidence of epileptic disorders or withdrawal seizures;
13. History of substance withdrawal delirium;
14. Breast-feeding woman, or a positive result of urine pregnancy test (at screening), or plan to become pregnant during the course of the trial (females only);
15. Pending legal charges with the potential for incarceration, probation, or parole;
16. Homelessness (less than 2 months stable residence);

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17. Participation in a clinical trial during the 3 months prior to screening.

Test Product, Dose, Mode of Administration, Batch No(s):

SCH 900435 batch number [redacted] (BC022 design 1) and placebo batch number [redacted] (BC022 design 2) were prepared as white tablets for oral administration. Each tablet contained 4 mg SCH 900435 or placebo. Formulation of the investigational product and placebo were indistinguishable with respect to appearance, shape, smell and taste. Storage conditions were to be 2-25 ºC.

On Day 1, subjects were to receive 12 mg SCH 900435 (or placebo) BID. Three oral tablets were to be taken in the morning within 2 hours after breakfast and in the evening within 2 hours after a meal.

The investigator was to attempt to keep all subjects on the dose regimen of 12 mg BID. However, in the event of intolerable adverse events (AEs) that would otherwise lead to the subject's premature discontinuation from the trial, the investigator could offer a dose reduction to 8 mg BID.

Duration of Treatment:

The trial included a screening period of up to 7 days, a treatment period of 84 days, and a follow-up period of 30 days.

Criteria for Evaluation:

Primary endpoint:

- Percentage of heavy drinking days, defined as days with ≥ 5 standard drinks for men and ≥ 4 standard drinks for women assessed by timeline follow back method (TLFB) (for definition of a standard drink, see List of Definitions).

Secondary endpoints:

- Amount of drinking: drinks per day and drinks per heavy drinking day (TLFB);
- Relapse: time to first relapse into heavy drinking and time to first drink (TLFB);
- Abstinence: cumulative abstinence duration; percentage of abstinent days; percentage of complete abstinence (TLFB);
- Safety and tolerability: serious adverse events (SAEs), clinical examination, clinical laboratory, ECG, ophthalmologic assessments;
- Number of relapses; alcohol relapse is defined as either a daily alcohol intake of five or more drinks for males and four or more drinks for females or an overall consumption of 14 drinks or more per week during at least 4 weeks (TLFB);
- Number of 'lapses'; alcohol lapse is defined as any episode of alcohol consumption not classified as relapse;
- Responders (defined as subjects with 50% reduction of heavy drinking days);
- Cumulative non-heavy drinking days (TLFB);
- Global functioning (Clinical Global Impression [CGI]-severity, CGI-change);
- Quantification of thoughts about alcohol and drinking behavior (Obsessive-Compulsive Drinking Scale [OCDS]);
- Craving visual analog scale (VAS);
- Mood (VAS);
- Motivation (VAS).

Optional research component

- Pharmacogenetics assessment for subjects who signed separate informed consent.

Statistical Methods:

The primary efficacy endpoint was the percentage of days of relapse into heavy drinking, as derived from the

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Alcohol TLFB interview. Percentage was calculated based on number of heavy drinking days divided by total number of days in the given 2-week interval. The statistical analysis for the comparison of SCH 900435 to placebo was a mixed model repeated measurements (MMRM) analysis, including the fixed effects of treatment, biweekly periods, and (pooled) centers. In the model the bi-weekly period was a repeated measure and the within-subject errors were modeled using an unstructured covariance matrix. The sensitivity of the analysis was checked by evaluating the treatment by period interaction. The statistical test of SCH 900435 compared to placebo was performed two-sided at an overall $\alpha = 0.05$ significance level; the interim analysis was performed at a significance level of $\alpha = 0.003$ and the final analysis at $\alpha = 0.047$.

The secondary parameters derived from the TLFB interview as percentage of abstinent days and number of drinks per (heavy) drinking day were analyzed using the same strategy as the primary efficacy endpoint. The OCDS, VAS, and CGI -Severity were also analyzed with a MMRM analysis. Complete abstinence, subjects with non-heavy drinking days, subjects with no drinking days at all (all TLFB); and CGI Therapeutic Effect were analyzed with a logistic regression analysis. Treatment comparison of time to first relapse into heavy drinking and time to first drink was summarized using a Kaplan-Meier plot and analyzed with a Cox proportional hazards model. Summary tables were generated for all efficacy parameters.

Safety was evaluated by summarizing the number of subjects who encountered any emerging SAE in general or a visual AE in particular. Differences between SCH 900435 and placebo for laboratory measurements were evaluated by summarizing subjects with notable shifts and subjects with values outside the safety ranges. Vital signs parameters were also evaluated by the number of subjects who encountered values outside the safety ranges. ECG and ophthalmologic endpoints were evaluated using frequency tables and summary statistics.

Sample size considerations:

Assuming an effect size of 0.32 and a correlation between assessments of 0.7, 150 subjects per treatment group would ensure this study had a 90% power to detect a difference of 10% in heavy drinking days between SCH 900435 and placebo.

Interim Analysis:

Subject enrollment was interrupted in January 2010 and, following protocol amendment 3, an interim analysis was conducted after all recruited subjects had completed the treatment period and data validation had been finalized. The primary objective of the analysis was to determine if the trial should be stopped for futility. The threshold for futility was set at a conditional power of 40%. The interim analysis was executed by a statistician who was not involved with the study, and the review of the results was undertaken by the Standing Internal Data Monitoring Committee (siDMC). The siDMC was to consider the trial futile if the p-value at interim was not below 0.2074 and with the effect size in the appropriate direction, ie, favoring active treatment. Due to the interim analysis $\alpha = 0.003$ was spent, leaving a significance level of $\alpha = 0.047$ at study end for the primary endpoint.

SUMMARY-CONCLUSIONS:

RESULTS: Based on the interim analysis, the trial was stopped early for futility on 25 June 2010. At that point, 141 of the planned 300 subjects had been enrolled and completed their last visit in the trial.

Disposition, demographics and baseline characteristics: A total of 141 adult subjects were treated, 75 in the SCH 900435 group and 66 in the placebo group. All received at least one dose of study medication and were therefore included in the all-subjects-treated group (AST). Of these, a total of 33 subjects discontinued, 22 (29%) in the SCH 900435 group and 11 (17%) in the placebo group, though individual reasons for discontinuation were not notably different between groups. Treated subjects were between the ages of 26 and 65 years (mean, 49.3 years), all 141 (100%) subjects were white, and 104 (74%) of treated subjects were male.

Efficacy: The primary efficacy endpoint was the percentage of days of relapse into heavy drinking, as derived from the TLFB interview, calculated per 2 week assessment. MMRM analysis resulted in least squares (LS) mean values of 18.7 (95% CI: 14.5, 23.0) and 16.3 (95% CI: 11.8, 20.8) for SCH 900435 and placebo treatment groups, respectively. The difference in LS means of 2.4 with a 95% confidence interval of (-3.4, 8.2) of SCH 900435 versus placebo was not statistically significant ($p = 0.41$). The mean (standard error) percentages of heavy drinking days per 2 week interval are shown in the figure below.

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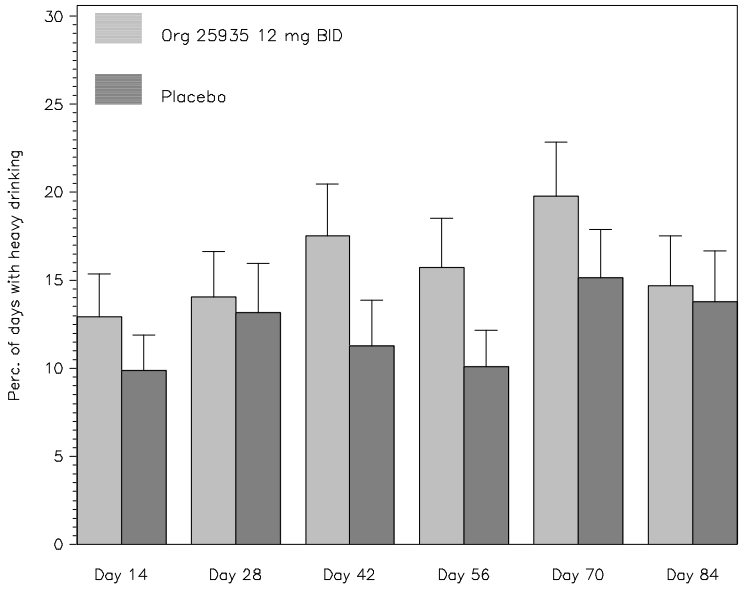

Mean (Standard Error) Percentage of Heavy Drinking Days Per 2-week Interval (Modified Intent-to Treat Group)

Source data: S1520_prhedays_Graph.rtf

With regard to secondary efficacy endpoints, no statistically significant effect was found between SCH 900435 and placebo treatment groups for other TLFB-derived parameters (amount of drinking, time to first relapse into drinking and time to first drink, abstinence, number of relapses and lapses, cumulative number of subjects with non-heavy drinking days). Further, no statistically significant difference was found between SCH 900435 and placebo treatment groups on OCDS, VAS, or CGI, with the following exceptions:

-Placebo showed a significant benefit over SCH 900435 on change from baseline for the OCDS obsessive thoughts subscale at Day 84 ($p = 0.02$);

-The SCH 900435 group was significantly more improved over the placebo group on VAS mood at Day 3 ($p < 0.01$), Day 56 ($p < 0.01$), and Day 84 ($p = 0.05$).

-SCH 900435 showed a significant advantage over placebo on CGI-change at Day 7 ($p = 0.03$).

Note that these other secondary endpoint analyses were conducted without adjustment for multiplicity; results should therefore be interpreted with caution.

Safety:

A total of 65 (87%) SCH 900435 and 53 (80%) placebo-treated subjects experienced at least one AE. No subjects died during the study period or the follow-up period. SAEs were reported for 10 (13%) of subjects treated with SCH 900435 and 12 (18%) of subjects treated with placebo; all but one of the SAEs (a hypertensive crisis in a SCH 900435-treated subject considered possibly related to study medication) were considered by the investigator to be unlikely to be related or unrelated to study medication. In total 6 (8%) SCH 900435 and 3 (5%) placebo-treated subjects discontinued the study due to an AE. Overall, the most frequently reported treatment-emergent AEs occurring in the SCH 900435 treatment group were fatigue 19 (25%), dizziness 15 (20%), headache 13 (17%), and nasopharyngitis 11 (15%); and in the placebo treatment group nasopharyngitis (27%) and headache (23%) were the most commonly reported.

A total of 27 (36%) SCH 900435 and 7 (11%) placebo-treated subjects experienced a visual AE. The most common of these in the SCH 900435 treatment group was photophobia. The large majority of visual events in the SCH 900435-treated group were mild (79%) and resolved by the time of the last assessment (96%); 11% of visual AEs reported by SCH 900435-treated subjects led to a dose reduction, though none led to

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discontinuation. No major differences between treatments were found in post-baseline visual field abnormalities and color/hue vision. A higher percentage of SCH 900435-treated subjects experienced post-baseline worsening in visual acuity (left eye: 12.1% SCH 900435-treated versus 4.0% placebo-treated; right eye: 15.5% SCH 900435-treated versus 2.0% placebo-treated). Improvements in acuity were also noted (left eye: 12.1% SCH 900435-treated versus 18.0% placebo-treated; right eye: 15.5% SCH 900435-treated versus 18.0% placebo-treated). Changes in ophthalmology test results were not reported for subjects with visual adverse events, with two exceptions. One subject with vision blurriness failed the color test at endpoint; one subject reporting visual spots showed an abnormality on visual field testing at endpoint. In both cases, the reported adverse events resolved at least two months prior to testing and the test findings themselves were not reported as adverse events, so the clinical relevance of the findings is unlikely.

Evaluation of notable laboratory shifts showed treatment group differences for the alanine transaminase (ALAT) parameter (upward shift in 28.4% of SCH 900435-treated subjects and 15.4% of placebo-treated subjects), cholesterol (upward shifts in 22.5% of SCH 900435-treated subjects and 40.6% of placebo-treated subjects), MCV (downward shift in 23.0% of SCH 900435-treated subjects and 1.6% of placebo-treated subjects), erythrocyte count (downward shifts in 5.6% of SCH 900435-treated subjects and 14.1% of placebo-treated subjects, upward shifts in 11.3% of SCH 900435-treated subjects and 1.6% of placebo-treated subjects), hemoglobin (downward shifts in 23.9% of SCH 900435-treated subjects and 4.7% of placebo-treated subjects), and neutrophils (upward shifts in 21.7% of SCH 900435-treated subjects and 14.1% of placebo-treated subjects).

Evaluation of markedly abnormal laboratory values showed that more SCH 900435-treated subjects had ALAT and aspartate transaminase (ASAT) values above the safety range (ALAT: 6.8%; ASAT: 10.8%) than did placebo-treated subjects (ALAT: 1.5%; ASAT: 3.1%). For the cholesterol total parameter subjects with values above the safety limits were 30.2% (placebo) and 11.4% (SCH 900435). For hematocrit the subjects treated with SCH 900435 showed values below the safety limits more often than subjects treated with placebo, 11.3% and 4.7%, respectively. For monocytes and neutrophils the SCH 900435-treated subjects showed a value above the safety limits more often than placebo-treated subjects. For monocytes this was 13.0% versus 6.3% for placebo-treated subjects, and for neutrophils this was 13.0% versus 7.9% for placebo-treated subjects.

Special evaluation was undertaken in the trial for liver laboratory parameters, given that excessive alcohol use is associated with liver damage. Based on the FDA guidance, an evaluation was made of the liver enzymes ALAT, ASAT, alkaline phosphatase, total bilirubin, and gamma-glutamyl-transferase (GGT). A total of 5 SCH 900435-treated subjects had a maximum ALAT value above 3*upper limit of normal (ULN): 1 of these was above 5*ULN, and 1 was above 8*ULN. For the placebo group, there was only 1 subject who had a maximum value above the 3*ULN. For ASAT, 8 SCH 900435-treated subjects had a maximum value above 3*ULN: 3 of these were above 5*ULN, and 1 was above 10*ULN. For the placebo treatment group, 1 subject had a maximum value above the 3*ULN and one had a maximum value above 5*ULN. For other liver laboratory parameters, there were no marked differences between the SCH 900435 treatment group and the placebo treatment group.

[redacted] Increases of transaminase (ASAT, ALAT), alkaline phosphatase, and GGT plasma values suggested acute cholestatic hepatitis. The SAE was unlikely related to the study drug in the opinion of the investigator and possibly related according to the sponsor. Risk factors for this SAE include pre-existing alcohol-induced liver damage (i.e., markedly high baseline liver parameters).

There were no notable treatment group differences for vital sign summary statistics, shifts, or values outside the safety ranges. There were no clinically relevant ECG changes associated with SCH 900435 treatment and there were no notable treatment group differences on mean change from baseline for ECG parameters.

CONCLUSIONS*:*

The following conclusions can be drawn from this study:

- Based on a planned interim analysis, the trial was stopped early for futility. At that point, 141 of the planned 300 subjects had been enrolled and completed their last visit in the trial.
- No statistically significant difference was observed between SCH 900435 and placebo on the primary efficacy endpoint, which was percentage of heavy drinking days as recorded by the TLFB method. The difference in LS means of 2.4% with a 95% confidence interval of (-3.4%,8.2%) of SCH 900435 versus placebo was not statistically significant (p=0.41). Further, there were no significant treatment group differences on other TFLB endpoints including amount of drinking, time to first relapse to heaving

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drinking, and cumulative duration of abstinence.

- In general, SCH 900435 was well tolerated. The most frequent AEs associated with SCH 900435 treatment, but not placebo treatment, were fatigue (SCH 900435: 25%; placebo: 5%) and dizziness (SCH 900435: 20%; placebo: 14%). Visual AEs were reported by 27 (35%) SCH 900435 subjects and 7 (11%) placebo subjects. The large majority of visual events in the SCH 900435-treated group were mild (79%) and resolved by the time of the last assessment (96%); 11% of visual AEs reported by SCH 900435-treated subjects led to a dose reduction, though none led to discontinuation and none were associated with clinically relevant ophthalmology findings. These findings are highly consistent with previous SCH 900435 trials and provide further evidence that SCH 900435 treatment is associated transient, subjective visual AEs.
- Ophthalmology parameters (acuity, color, visual field) were similar between groups, though a higher percentage of SCH 900435-treated subjects experienced post-baseline worsening in visual acuity (left eye: 12.1% SCH 900435-treated versus 4.0% placebo-treated; right eye: 15.5% SCH 900435-treated versus 2.0% placebo-treated).
- There were no clinically relevant treatment group differences for vital signs or ECG parameters.
- Although SCH 900435 was associated with a higher percentage of subjects with ALAT/ASAT values significantly above normal limits compared to placebo, causal attribution for these findings is challenged by the nature of the underlying disease. The majority of subjects with high values, regardless of treatment group, also showed high values at baseline and/or were drinking heavily during the trial. These confounds, combined with the fact that liver issues have not been identified in any other human population studied to date (healthy volunteers, stabilized schizophrenic subjects, subjects with panic disorder), challenge a simple interpretation of the liver laboratory abnormalities in the current trial as drug-related.

Date of the Report: 11 NOV 2011

[redacted]