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 SYNOPSIS

Title of Study:	A Phase 2a, Multiple-Dose, Placebo-Controlled, Randomized, Two-Way Crossover Study to Assess the Efficacy of Preladenant (SCH 420814) in Reducing Antipsychotic-Induced Extrapyramidal Symptoms Among Subjects With Schizophrenia And Schizoaffective Disorders (Protocol P04628)	
Investigator(s):	Multicenter	
Study Center(s):	5 Study Centers in FRANCE and GERMANY	
Publication(s):	None	
Studied Period:	14 AUG 2006 to 06 MAR 2008	**Clinical Phase:** 2a

Objective(s):

Primary Objective: The primary objective of this proof-of-concept (POC) study was to assess if antipsychotic-induced extrapyramidal symptoms (EPS) can be reduced by SCH 420814 at the dose of 25 mg twice a day (BID).

Secondary Objectives:

1. To assess the safety and tolerability of SCH 420814 as an adjunct to antipsychotic therapy
2. To document the pharmacokinetics of SCH 420814

Methodology: This was a randomized, placebo-controlled, third-party blind, two-way crossover, study to evaluate the clinical effect of preladenant 25 mg BID in subjects with schizophrenia or schizoaffective disorder with EPS. Subjects received study medication during two 15-day Treatment Periods separated by a 2- to 3-week washout period. All subjects were randomized to 1 of 2 treatment sequences (preladenant/placebo or placebo/preladenant) and received preladenant 25 mg orally BID for 15 days and matching placebo orally BID for 15 days. Subjects continued taking a stable dose of antipsychotic medication throughout the study. Efficacy was assessed using the Extrapyramidal Symptom Rating Scale (ESRS). The Positive and Negative Syndrome for Schizophrenia (PANSS) scale was also assessed.

This study was conducted in compliance with Good Clinical Practice.

Number of Subjects: This study was designed to enroll 24 subjects. Eleven subjects (4 female, 7 male) between the ages of 25 and 61 years of age (mean = 41.5 years) were randomized to two treatment sequences (SCH 420814/placebo [4 subjects] or placebo/SCH 420814 [7 subjects]); two female subjects discontinued during the first treatment period while receiving placebo.

Diagnosis and Criteria for Inclusion:

Subject Inclusion Criteria:

1. Males or females of 18 years (included) of age and a maximum of 65 years old and having a Body Mass Index (BMI) of 17 to 31. BMI = weight (kg)/height (m^2).
2. Subjects with Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria of schizophrenia and schizoaffective (depressive type) disorder with antipsychotic-induced extrapyramidal symptoms (EPS), such as parkinsonism and/or akathisia and/or dystonia and/or tardive dyskinesia (TD) based on developed ESRS criteria.
   a. An ESRS score of 2 on 2 items or a score of 3 or greater on one item was required to establish a presence of parkinsonism.
   b. An ESRS score of 2 on 2 items or a score of 3 or greater on one item was required to establish a presence of dystonia.
   c. An ESRS score of 2 on 2 items or a score of 3 or greater on one item was required to establish a presence of TD.
   d. An ESRS score of 3 or greater on the two items was required to establish a presence of akathisia.
   e. Subjects must have had a minimum total score on the ESRS of 8.
3. To enter the treatment phase of the study, subjects must have been receiving neuroleptics (haloperidol, cyamemazine, tiapride, sulpiride, levomepromazine, perphenazine, perazine, melperone, promethazine, pipamperone, chlorprothixene, chlorpromazine, or risperidone), at a stable dosage for at least 7 days prior to enrollment. Other neuroleptics that have caused EPS were considered after discussion between sponsor and site.

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4. Clinical laboratory tests (complete blood count [CBC], blood chemistries, and urinalysis) must have been within normal limits or clinically acceptable to the investigator/sponsor. All subjects should have had their liver function tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALK-P], gamma-glutamyl transpeptidase [GGT], and total bilirubin [T-BIL]) within normal limits on screening.
5. Drug screen for drugs with a high potential for abuse must have been negative.
6. Subjects must have been free of any clinically significant disease other than schizophrenia and schizoaffective (depressive type) disorder that would interfere with the study evaluations or procedures.
7. Subjects must have had a level of understanding sufficient to communicate with the research staff and to cooperate with all tests and examinations required by the protocol and have been able to adhere to protocol restrictions and schedules.
8. Subjects must have been able to understand the nature of the study and must have been willing to sign an informed consent (required for each patient and/or the patient's authorized legal representative) prior to study enrollment.
9. Physical exam must have been within normal limits or clinically acceptable to the investigator/sponsor (except signs and symptoms of schizophrenia and schizoaffective disorder).
10. Females must have had a follicular stimulating hormone (FSH) $\geq$40 international units (IU)/L and last menses or surgically sterilized must have been greater than 12 months.
11. The electrocardiogram (12-lead recorded at 25 mm/s and reporting ventricular rate and PR, QRS, QT, and QTc intervals) must have been clinically acceptable.

Subject Exclusion Criteria: Subjects who met the following criteria were excluded:

1. Subjects who had a history of any clinically significant local or systemic infectious disease within 4 weeks prior to initial treatment administration.
2. Subjects who had participated in a clinical trial of an investigational drug within 60 days prior to the start of the study.
3. Subjects who had a clinically significant history of food or drug allergy.
4. Subjects who had donated blood within the preceding 90 days.
5. Subjects with circulating human immunodeficiency virus (HIV), Hepatitis C antibodies, or Hepatitis B surface antigen.
6. Subjects who were allergic to SCH 420814 or were allergic to any of the excipients in SCH 420814 capsules (citric acid, lactose monohydrate, croscarmellose sodium, magnesium stearate [nonbovine, vegetable grade], Federal Food Drug and Cosmetic [FD&C] blue, titanium dioxide, gelatin-national formulary [NF]).
7. Females who were not surgically sterilized or postmenopausal.
8. Male subjects who were sexually active and who did not agree to use a barrier method of birth control during the study.
9. Subjects with severe/uncontrolled hypertension were excluded. Subjects with hypertension well controlled on a stable dose of standard antihypertensive medication for at least 4 weeks before randomization were eligible.
10. Subjects with history of coronary artery disease including myocardial infarction (MI), or cerebrovascular disease (stroke, transient ischemic attack [TIA]), or peripheral arterial disease.
11. Subjects with atrioventricular (AV) block, sick sinus syndrome, congestive heart failure, or subjects with ECGs consistent with ischemic heart disease, or significant Q waves.
12. Subjects with a history of any of the following: seizures, alcohol/drug dependence, previous neurosurgery.
13. Subjects with DSM-IV criteria of dementia (except due to schizophrenia and schizoaffective disorder), or individuals who in the opinion of the investigator were not able to understand and/or comply to the study procedures and/or the instructions of the staff or were socially incapable to participate in the study.
14. Individuals who did not comply with the requirement that he or she should not have used any drugs (except acetaminophen and other allowed medications) within 2 weeks prior to the study nor alcohol (wine, beer) within 72 hours prior to drug administration.

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15. Subjects who were judged clinically to be at suicidal risk too serious to be included in this study.
16. Subjects who had received electroconvulsive therapy (ECT) within 30 days before randomization.
17. Subjects who were currently taking clozapine were excluded from study participation.

Test Product, Dose, Mode of Administration, Batch No: SCH 420814 25 mg (1 x 25 mg; [Batch Number: [redacted] BID x 13 days, oral. A single dose was given on the AM of Day 14.

Supplies were provided in bulk packaging.

Duration of Treatment: Two treatment periods, each period 15 days

Reference Therapy, Dose, Mode of Administration, Batch No: Matching placebo capsules (1 x 25 mg; [Batch Number: [redacted] BID x 13 days, oral. A single dose was given on the AM of Day 14.

Supplies were provided in bulk packaging.

Criteria for Evaluation:

Efficacy: The primary efficacy endpoint is the lowest ESRS total score within the 6-hour range on Day 14.

The secondary efficacy endpoints include each lowest subscore within the 6-hour range on Day 14, each subscore at Hours 1, 2, 3, 4, 5, and 6 on Day 14, the total score at Hours 1, 2, 3, 4, 5, and 6 on Day 14, and the time-weighted average total score on Day 14.

Pharmacokinetic: For those subjects who completed earlier versions of the protocol, the derived pharmacokinetic (PK) parameters (area under the curve [AUC] and maximal concentration [Cmax]) are listed and concentration data tabulated by each sampling time. To enhance enrollment, subjects enrolled according to Amendment 3 only had sparse pharmacokinetic sampling.

Exploratory Analyses: The percent improvement from baseline in ESRS scores on Day 14 (ie, 20% improvement, 30% improvement, etc) along with the 95% confidence interval is summarized by the treatments. A regression type analysis was to be carried out to evaluate a possible relationship between the efficacy endpoints and SCH 420814 concentrations/PK parameters.

Statistical Methods: The data was to be statistically analyzed via an analysis of variance model for crossover designs extracting the effects due to subjects, treatment (SCH 420814 vs placebo), period, and sequence. Point estimate along with 95% confidence interval are provided for the difference of the ESRS total scores between SCH 420814 and placebo. The baseline ESRS score (defined as the lowest ESRS score within the 6-hour range measured on Day –1) were analyzed similarly to assess the compatibility between the two treatment groups at baseline.

Secondary efficacy endpoints were analyzed via an analysis of variance model for crossover designs extracting the effects due to subjects, treatment (SCH 420814 vs placebo), period, and sequence.

Although an interim analysis was planned after 12 subjects completed treatment, an interim analysis was conducted on 21 AUG 2007 after only 9 subjects completed treatment because of the low enrollment. Based on the results of the interim analysis, the decision was made to continue enrolling subjects, but the study was terminated on 06 MAR 2008 because no subjects had enrolled after the interim analysis.

SUMMARY-CONCLUSIONS:

RESULTS:

Efficacy: No efficacy conclusions could be drawn in this study because the study was terminated before a sufficient number of subjects were enrolled to create an efficacy-evaluable data set.

Safety: Treatment with preladenant 25 mg BID for up to 14 days was generally well tolerated in subjects with schizophrenia or schizoaffective disorder experiencing antipsychotic-induced extrapyramidal symptoms. No severe adverse events were reported during treatment with preladenant. One subject was hospitalized during placebo treatment. No deaths occurred during the study.

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CONCLUSIONS:

- No efficacy conclusions could be drawn in this study of subjects with schizophrenia and schizoaffective disorders because of the small number of subjects enrolled and the early termination of the study.
- Treatment with preladenant 25 mg BID for up to 14 days was well tolerated in subjects with schizophrenia or schizoaffective disorder experiencing antipsychotic-induced extrapyramidal symptoms.

Date of the Report: 29 OCT 2009