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:	Study of the Efficacy and Safety of SCH 486757 in Subjects With Chronic Idiopathic Cough (Protocol No. P04887)	
Investigator:	[redacted]	
Study Center:	[redacted] UK	
Publication(s):	None	
Studied Period:	19 JUN 2007 to 29 NOV 2007	**Clinical Phase:** 2

Objectives:

Primary Objective: To evaluate the effectiveness of SCH 486757 in reducing cough reflex sensitivity as determined by a capsaicin challenge.

Key Secondary Objective: To evaluate the effectiveness of SCH 486757 in reducing severity of cough as determined by 24-hour cough counting.

Secondary Objectives:

- To evaluate the effectiveness of SCH 486757 in reducing the severity of cough as determined by subjective measures (daily cough scores, visual analog scores [VAS], Leicester Cough Questionnaire [LCQ], cough frequency, lack of sleep, interference with daily activities, and response to treatment from diary evaluations; and
- To estimate the exposure to SCH 486757 administered at a dose of 2 x 50 mg twice daily (BID).

Methodology: This was a Phase 2, randomized, double-blind, placebo-controlled, crossover, single center study of SCH 486757 in subjects with chronic idiopathic cough (CIC). The washout was 2 weeks, a period which corresponded to at least six half-lives of the drug. The study was conducted in conformance with the principles of Good Clinical Practice.

This study assessed the efficacy of SCH 486757 in three different ways: (1) capsaicin challenge; (2) 24 hours of cough counting; and (3) subjective assessment using a daily diary, VAS, and LCQ.

1. Capsaicin challenge was used to measure cough reflex sensitivity because inhalation of capsaicin induces cough in a dose-dependent, reproducible manner. Increasing concentrations of inhaled capsaicin were given until a dose was reached that induced ≥5 coughs in 15 seconds (C5) following inhalation. With therapy, an increase in the dose needed to reach C5 was expected and, consequently, a decrease in cough reflex sensitivity.
2. Coughs were counted using a digital portable cough counter that has been used and validated in counting coughs in a variety of conditions and settings. The cough counter consists of two components: a recorder and a chest wall lead. It identifies cough by a combination of sound frequency and chest wall movement.
3. Subjective evaluation was performed via a diary in which subjects rated cough severity twice daily, cough frequency twice daily, lack of sleep once daily in the morning, interference with daily activities once daily in the evening, and how cough has affected me on a VAS twice daily. The LCQ is a validated instrument for evaluating the impact of chronic cough on quality of life. This 19-item questionnaire has three components that measure the physical, social, and psychological effects of chronic cough.

Number of Subjects: Thirty subjects were planned, and 31 subjects were randomized. Of these 31 subjects, 23 completed both treatment arms, and 8 discontinued the study early (SCH 486757/placebo, 3 subjects and placebo/SCH 486757, 5 subjects).

Diagnosis and Criteria for Inclusion: Male and female subjects 18 to <65 years old with a history of a dry cough for >6 months. The following inclusion criteria had to be met to be included in the trial:

1. By history, evaluation of gastroesophageal reflux disease was done and ruled out by a minimum of an 8-week trial of antacid therapy (with a proton-pump inhibitor [PPI] given twice daily) with no clinical response in cough.
2. By history, if there were clinical signs and symptoms of postnasal drip, these signs and symptoms were to have been treated with a combination of an antihistamine and decongestant for a minimum of 8 weeks with no clinical response in cough.

Title of Study:	Study of the Efficacy and Safety of SCH 486757 in Subjects With Chronic Idiopathic Cough (Protocol No. P04887)

3. By history, if there were clinical signs and symptoms of asthma, these signs and symptoms were to have been treated with a combination of an inhaled steroid and a short-acting beta-agonist for a minimum of 8 weeks with no clinical response in cough.

4. After crossover to the second treatment period, the baseline values for both cough rate and capsaicin challenge (ie, C5), had to be within one doubling concentration from the initial Baseline for Treatment Period 1. If the baseline values were not within one doubling concentration, the subject could be reevaluated at a later time point.

Exclusion Criteria:

1. Subjects with current evidence of clinically significant pulmonary (especially conditions that involved coughing), hematopoietic, cardiovascular, hepatic, renal, neurologic, psychiatric, autoimmune, or other disease that precluded the subject's participation in the study. In particular, diabetics, uncontrolled hypertensives, and subjects with clinically significant cardiomyopathy, prostatic hypertrophy, glaucoma, seizure disorders, and psychiatric disorders were to be excluded from participation in this study.

2. Subjects with asthma or chronic obstructive pulmonary disease who required chronic use of inhaled or systemic corticosteroids.

3. Subjects with a history of hypotension or orthostatic hypotension.

4. Subjects who received concurrent prohibited medications unless they observed the washout period prior to the baseline visit (Visit 1). These medications included opioid- and non–opioid-containing cough suppressants and potent CYP3A inhibitors, such as ritonavir, ketoconazole, and clarithromycin. Subjects receiving angiotensin converting enzyme (ACE) inhibitors or monoamine oxidase inhibitors (MAOIs) were to be excluded from the study.

5. Subjects with a history of allergies to more than two classes of medications.

6. Subjects with a history of hypersensitivity to the study medications or to their excipients.

7. Subjects who used any study medication, including placebo, in an investigational protocol within 30 days prior to the baseline visit (Visit 1).

8. Women who were breastfeeding, pregnant, or intended to become pregnant.

9. Subjects who were family members of the investigational study staff involved with this study.

10. Subjects previously enrolled into this study (ie, signed informed consent).

11. Subjects whose ability, in the opinion of the investigator or designee, to provide informed consent was compromised.

12. Subjects with a history of noncompliance with medications or treatment protocols or with a history of drug abuse.

13. Current smokers, ex-smokers who stopped smoking in the previous 6 months, or subjects with a cumulative smoking history >10 pack-years were to be excluded. (Pack-years is a way to measure the amount a person has smoked over a long period of time. It is calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person has smoked, eg, a 10 pack-year history is equal to smoking 1 pack per day for 10 years or 2 packs per day for 5 years, etc.)

Test Product, Dose, Mode of Administration, Batch No.: SCH 486757 2 x 50-mg capsule administered orally BID. Batch number was [redacted]

Duration of Treatment: Two weeks of treatment followed by a 2-week washout period and 2 weeks of crossover treatment.

Reference Therapy, Dose, Mode of Administration, Batch No.: 2 x matching placebo (SCH 3445) capsule administered orally BID. Batch number was [redacted]

Title of Study:	Study of the Efficacy and Safety of SCH 486757 in Subjects With Chronic Idiopathic Cough (Protocol No. P04887)

Criteria for Evaluation:

Primary Efficacy Endpoint: Change from Baseline in cough reflex sensitivity as assessed by log10 C5 resulting from a capsaicin challenge after 2 weeks of treatment. A capsaicin challenge was performed on the first day (before the first dose was given) and on the last day of each 2-week treatment period.

Key Secondary Efficacy Endpoint: Change from Baseline in hourly cough rate over 24 hours (using an automated cough counter) after 2 weeks of treatment. Baseline was measured as the total number of coughs on the first day (first 24-hour evaluation) of each 2-week treatment period and compared with the total number of coughs on the last day of each 2-week treatment period.

Secondary Efficacy Endpoints: Changes from Baseline in daily cough scores, VAS, LCQ, cough frequency, lack of sleep, interference with daily activities, and response to treatment from diary evaluations.

Statistical Methods:

Efficacy Analyses: The primary efficacy endpoint, the change from Baseline in log10 C5, was analyzed using an analysis of variance (ANOVA) model extracting sources of variation due to treatment and period as fixed effects and subject as a random effect. Treatment was compared with placebo using the least squares means from the ANOVA at alpha = 5%, two-sided. If the comparison with placebo was significant for the primary variable, SCH 486757 was to be compared with placebo for the key secondary variable. If the results for the key secondary variable were significant, then all the other secondary variables were to be tested at unadjusted alpha = 0.05. Means and 95% confidence intervals of the differences between the treatments were derived. The key secondary efficacy endpoint, change from Baseline in the hourly cough rate, as well as all other secondary endpoints were to be analyzed in the same fashion as the primary endpoint.

Missing Data Handling: If the cough count at the highest dose of capsaicin was missing, the value of 5 was used. Impact analyses were performed when the capsaicin dose for the missing value was replaced with the lowest C5 recorded across all visits for that subject.

Safety Analyses: Descriptive statistics were to be provided for safety data. No inferential analysis of safety data was planned. The number of subjects reporting any adverse events, occurrence of specific adverse events, and discontinuation due to adverse events were to be tabulated by treatment. Laboratory data were to be listed, and values outside the normal ranges were to be flagged. The safety endpoint of Stanford Sleepiness Scale (SSS) scores was to be analyzed using the same ANOVA described for the efficacy analyses.

SUMMARY-CONCLUSIONS:

RESULTS:

Efficacy:

Primary Efficacy Endpoint: The change from Baseline in capsaicin challenge C5 (log10 transformed) performed at Visits 2, 4, 6, and 8 was the primary efficacy endpoint. Baseline mean log10 C5 dilution was approximately 0.86. The mean log dilution changes from Baseline at Day 14 were +0.10 for subjects administered SCH 486757 and -0.01 for placebo subjects. The difference between the two treatments of 0.11 (18%) was not statistically significant (P = 0.512). Because the primary variable did not show a statistically significant difference between active and placebo subjects, no other results should be considered statistically significant at P <0.05.

Key Secondary Efficacy Endpoint: The key secondary efficacy endpoint was the change from Baseline in hourly cough rate over 24 hours. At Day 14, subjects administered SCH 486757 showed a reduction of approximately 4 coughs/hour over 24 hours, a value equivalent to a 20% reduction from Baseline in 24-hour cough count compared with placebo subjects. The most differentiable results were noted during the daytime hours. Reduction in cough counts in subjects administered SCH 486757 appeared to be correlated with somnolence. At Day 14, subjects who reported somnolence following administration of SCH 486757 showed a reduction of approximately 7.5 coughs/hour over 24 hours, a value equivalent to a 40% reduction from Baseline in 24-hour cough count compared with placebo. In comparison, subjects who did not report somnolence showed a reduction of approximately 2.1 coughs/hour over 24 hours, a value equivalent to a 2% reduction from Baseline in 24-hour cough count compared with placebo.

Secondary Efficacy Endpoints: Secondary efficacy endpoints included cough severity symptom scores, cough frequency symptom scores, lack of sleep scores, interference with daily activities scores, and how cough has affected me scores obtained from the daily diary card as well as LCQ scores. For cough severity symptom scores, subjects administered SCH 486757 showed a numeric superiority equivalent to 20% over placebo for the AM/PM, AM, and PM evaluations. For all other secondary endpoints, trends in favor of SCH 486757 compared with placebo were generally noted. LCQ scores showed more improvement than other subjective scores in subjects administered SCH 486757; these scores met the minimally important difference (MID).

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Pharmacokinetics: A two-compartment population PK model with first-order absorption and elimination was used to describe the pharmacokinetics of SCH 486757, using the rich data set obtained in the previous rising multiple-dose study (P03175). The model-predicted plasma SCH 486757 concentrations correlated well with the observed data in the present study. Individual area under the plasma concentration-time curve from time 0 to 12 hours (AUC[0-12 hr]) values ranged from 1468 to 6389 ng·hr/mL following 13 days of dosing with SCH 486757 100 mg BID. The intersubject variability in exposure obtained in this study was consistent with previous observations. There was a positive correlation between exposure to SCH 486757 and clinical efficacy as measured by the percent reduction from Baseline in cough count. No correlation between exposure and adverse events was observed.

Safety: Overall, 28 (90.3%) of 31 subjects reported treatment-emergent adverse events. The incidence of treatment-emergent adverse events was comparable between treatments: 23 (79.3%) of 29 subjects administered SCH 486757 and 19 (61.3%) of 31 placebo subjects reported treatment-emergent adverse events. All treatment-emergent adverse events were mild or moderate.

The most common treatment-emergent adverse event in subjects administered SCH 486757 was somnolence (n=14 [48.3%] vs n=2 [6.5%] in placebo subjects) followed by dizziness (n=5 [17.2%] vs n=1 [3.2%] in placebo subjects) and headache (n=5 [17.2%] vs n=6 [19.4%] in placebo subjects). Most of the common treatment-emergent adverse events in subjects administered SCH 486757 were considered treatment related.

There were no deaths or other serious adverse events. Two subjects discontinued from the study because of mild rhinitis that was considered unlikely related to treatment.

One subject each showed reversible increases in hepatic enzymes in Period 2 after 14 days' treatment with SCH 486757 or placebo; otherwise, no clinically significant changes in hematology, blood chemistry, or urinalysis parameters or vital signs occurred with either treatment. A prolonged QT interval corrected for heart rate (QTc) occurred in one subject at Day 14 after treatment with SCH 486757 in Period 2. Other subjects had no clinically significant changes in ECGs.

Subjects administered SCH 486757 showed a numerically greater increase in SSS score than placebo subjects at Day 14. The SSS findings confirm the higher incidence of somnolence reported as a treatment-emergent adverse event.

CONCLUSIONS:

- Subjects administered SCH 486757 100 mg BID for 2 weeks did not show a reduction from Baseline in cough reflex sensitivity as determined by a capsaicin challenge at Day 14 compared with placebo subjects.
- Subjects administered SCH 486757 100 mg BID for 2 weeks showed about a 20% reduction in 24-hour cough counts at Day 14 compared with placebo subjects. The reduction in cough count was noted mainly during the daytime hours.
- Subjects administered SCH 486757 100 mg BID for 2 weeks showed some reduction in cough severity symptom scores from Baseline at Day 14 compared with placebo subjects.
- Trends in favor of SCH 486757 compared with placebo were generally noted for all other secondary endpoints, including cough frequency symptom scores, lack of sleep scores, interference with daily activities scores, how cough has affected me scores, and LCQ scores. LCQ scores showed more improvement than other subjective scores; these scores met the MID.
- Estimated AUC(0-12 hr) values ranged from 1468 to 6389 ng·hr/mL following 13 days of dosing with SCH 486757 100 mg BID. The intersubject variability in exposure obtained in this study was consistent with previous observations.
- There was a positive correlation between exposure to SCH 486757 and clinical efficacy as measured by the percent reduction from Baseline in cough count. No correlation between exposure and adverse events was observed. Somnolence appeared to be correlated with efficacy as determined by the reduction in cough counts in subjects with somnolence after administration of SCH 486757.

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• SCH 486757 was generally safe and well tolerated; however, a higher incidence of somnolence was observed in 14 (48.3%) of 29 subjects in subjects administered SCH 486757, a finding that was confirmed by the SSS scores. In comparison, somnolence was observed in 2 (6.5%) of 31 placebo subjects. Somnolence appears to be a common side effect of the drug when administered at the 100-mg BID dose.	
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