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:	SCH 486757 vs Codeine and Placebo in Subjects With Persistent Postviral Cough (Protocol No. P03069)	
Investigator(s):	[redacted]	
Study Center(s):	16 sites in the United Kingdom, Latin America, and South Africa	
Publication(s):	None	
Studied Period:	17 OCT 2005 to 02 APR 2007	**Clinical Phase: 2**

Objectives:

Primary Objective: To assess the effectiveness of SCH 486757 (100 mg BID) in the reduction of the cough severity score compared with placebo.

Key Secondary Objective: To evaluate the reduction in the number of coughs per hour with SCH 486757 compared with placebo from the LifeShirt® system.

Secondary Objectives:

- To estimate the magnitude of exposure to SCH 486757 following 5 days of dosing of SCH 486757 100 mg BID.
- To evaluate the safety profile of SCH 486757 using subject-reported adverse events, electrocardiograms (ECGs), routine laboratory tests, vital signs evaluations, and the Stanford Sleepiness Scale (SSS).

Methodology: This was a Phase 2, randomized, multicenter, parallel-group, double-blind, double-dummy, placebo- and active-controlled study of SCH 486757 in subjects with persistent cough resulting from a recent viral upper respiratory infection (URI). The study was conducted in conformance with Good Clinical Practice.

Number of Subjects: The original target sample size was 150 subjects. Because of the difficulty in enrolling subjects, enrollment was terminated early. At study termination, 91 subjects had enrolled, and 89 subjects completed the study.

Diagnosis and Criteria for Inclusion: Male and female subjects with a diagnosis of recent viral URI who met the following inclusion criteria were selected for the study.

1. Subjects had to be 18 to <65 years of age, of either sex, and of any race.
2. At the Prescreening Visit (Visit 1), subjects had to have a history of a persistent cough resulting from a recent viral URI.
3. Subjects had to have had signs and symptoms indicative of a viral URI with an onset at least 14 days, but no more than 90 days, prior to the Prescreening Visit (Visit 1).
4. Subjects had to be sufficiently clinically symptomatic at the Screening Visit (Visit 2). Subjects had to demonstrate a score of at least 2 (moderate) in the cough severity score reflective of the previous 12 hours.
5. At the Baseline/Treatment Day 1 Visit (Visit 3), subjects had to demonstrate an average cough severity score of at least 2 (moderate) in the diary card for the AM and PM evaluations of the previous day and the AM evaluation of the visit day.
6. Subjects had to be in good health, free of any clinically significant disease, other than cough, that might interfere with the study schedule, evaluation, or interpretation of study-derived data.
7. Subjects had to be willing to give written informed consent and able to adhere to dose and visit schedules.
8. Clinical laboratory tests (complete blood count [CBC], blood chemistries, and urinalysis) and ECG had to be within normal limits or clinically acceptable to the investigator.
9. Female subjects of childbearing potential had to be using a medically accepted method of birth control prior to Prescreening (Visit 1) and agree to continue its use during the study and after the study until the next menses or had to have been surgically sterilized (eg, hysterectomy). Females of childbearing potential were to be counseled in the appropriate use of birth control while in this study. Females who were not currently sexually active had to agree and consent to use one of the medically accepted methods should they become sexually active while participating in the study.
10. Female subjects of childbearing potential had to have a negative serum pregnancy test (beta-human chorionic gonadotropin [hCG]) (prescreening sample).

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Test Product, Dose, Mode of Administration, Batch No(s): SCH 486757 2 x 50-mg capsule BID PO. Batch number for SCH 486757 50-mg capsules and for placebo codeine capsules was [redacted]

Duration of Treatment: Subjects were treated for 5 days.

Reference Therapy, Dose, Mode of Administration, Batch No(s): Codeine phosphate 1 x 30-mg capsule BID PO; matching placebo capsules to SCH 486757 and to codeine. Batch number for codeine phosphate capsules and for placebo SCH 486757 capsules was [redacted] Batch number for matching placebo capsules to SCH 486757 and to codeine phosphate was [redacted]

Criteria for Evaluation: All evaluations compared SCH 486757 vs placebo. Baseline value for the diary data was defined as the average of the following three readings: AM and PM of the Screening Day (Day -1) and AM of the Baseline/Treatment Day 1. Baseline for the key secondary efficacy endpoint (from the LifeShirt system) was defined as the 0- to 4-hour evaluation on Day -1.

Statistical Methods: The primary efficacy parameter was the change from Baseline in the cough severity score. The key secondary efficacy parameter was the reduction from Baseline in the number of coughs per hour from the LifeShirt system. An analysis of variance (ANOVA) extracting sources of variation due to treatment, sex, and study center was to be performed. Inferential treatment comparisons were to be based on the least squares means from the model at the 5% two-tailed level of significance. Comparisons of cough severity were to be made for SCH 486757 vs placebo and for codeine vs placebo. In addition, SCH 486757 was to be compared with codeine to assess relative efficacy. If SCH 486757 was significantly better than placebo in cough severity, then inferential comparisons were to be made in the reduction from Baseline in the number of coughs per hour (from the LifeShirt system) in a stepwise manner.

Primary Efficacy Endpoint: The primary endpoint for the study was the average AM/PM change from Baseline in cough severity score averaged over Days 1 through 5. The Days 1–5 average excluded the Day 1 AM evaluation because this evaluation was part of the baseline average. Baseline cough severity was defined as the average severity score of the three evaluations over Day -1 (AM, PM) and Day 1 (AM) prior to the first dose of randomized treatment.

Key Secondary Efficacy Endpoint: The key secondary variable was the reduction from baseline values in the number of coughs per hour (from the LifeShirt system) at 0 to 4 hours postdose on Day 1.

Secondary Efficacy Endpoints:

- Reduction from baseline value in the number of coughs per hour (from the LifeShirt system) at 0 to 8 hours postdose on each of Days 1 and 5 and the average of Days 1 and 5, and at 0 to 4 hours postdose on Day 5 and the average of Days 1 and 5.
- Average AM/PM change from Baseline in cough severity score for each of Days 1, 2, 3, 4, and 5, and separately for AM and PM at all time points.
- Onset of action based on the hourly reduction in cough counts and identification of the earliest sustained separation from placebo (from the LifeShirt system).
- Cough frequency, lack of sleep, interference with daily activities, VAS score, SSS score, and response to treatment from diary evaluations.

Pharmacokinetic Endpoint: To estimate the magnitude of exposure to SCH 486757 after 5 days of dosing.

SUMMARY - CONCLUSIONS:

RESULTS:

Efficacy:

Primary Efficacy Endpoint: For the average AM/PM change from Baseline in cough severity scores obtained from diary evaluations over Days 1 through 5, the codeine-treated group showed the largest mean decrease in scores from Baseline (-0.72). Both the SCH 486757- and codeine-treated groups were numerically better than placebo. The difference in cough severity scores between the SCH 486757-treated and placebo groups was -0.08 while the difference in scores between the codeine-treated and placebo groups was -0.23. Most of the improvement in the AM/PM average scores for the SCH 486757-treated group appeared to be driven by the AM assessments, an evaluation of the previous 12 hours.

Key Secondary Efficacy Endpoint: The baseline cough count measured by the LifeShirt system in the SCH 486757-treated group was higher than that in the other two groups because one subject had a high cough count at 0- to 4-hour time point. Another outlier in the placebo group had a high hourly cough count during the

first 4 hours following dosing on Day 1. Inclusion of these outliers skewed the means so that the number of coughs at Baseline and the magnitude of the changes in cough count from Baseline at Days 1 and 5 were larger for the SCH 486757-treated group than for either of the other two groups at every time point.

After excluding the two outliers, the baseline means were comparable among the three treatment groups. On Day 1, average change from Baseline in cough count for the SCH 486757-treated group remained numerically better than that for either the codeine-treated group or the placebo group. For the 0- to 4-hour average on Day 1, the SCH 486757-treated group had a 5.8 cough count reduction compared with a 2.3 reduction for the codeine-treated group and with a 0.9 reduction for the placebo group. On Day 5, the magnitude of cough count reduction was similar for the SCH 486757- and codeine-treated groups and was greater than that observed on Day 1.

Secondary Efficacy Endpoints:

- At 0 to 8 hours postdose on Days 1 and 5 and on the average of Days 1 and 5, reductions in cough counts measured by the LifeShirt system for all randomized subjects in the SCH 486757-treated group were numerically greater than those in the placebo group. At 0 to 4 hours postdose on Day 5 and on the average of Days 1 and 5, similar results were obtained. When the two outliers were excluded from the randomized population, the magnitude of the reductions in cough counts was less.

- Changes from Baseline in average AM/PM change from Baseline in cough severity scores obtained from diary evaluations decreased by day across the 5-day treatment period for both the SCH 486757- and codeine-treated groups. Similar results were obtained separately for the average AM cough severity scores.

- Onset of action based on the hourly reduction in cough counts and identification of the earliest sustained separation from placebo (from the LifeShirt system) was not observed; however, there was a larger numeric separation from placebo in the SCH 486757-treated group on Day 1 during the earlier part of the 8-hour interval compared with the latter part of that interval.

- Changes from Baseline in average AM/PM cough frequency scores and in average AM/PM scores on how cough affected subject were comparable in the SCH 486757-treated and placebo groups over Days 1 through 5. Similarly, average AM cough frequency, how cough affected subject scores, and lack of sleep scores and average PM cough frequency and how cough affected subject scores showed comparable changes from Baseline in the SCH 486757-treated and placebo groups over Days 1 through 5. In contrast, codeine-treated subjects had numerically greater improvement in average AM/PM and AM cough frequency scores, in average AM/PM, AM, and PM how cough affected subject scores, and in lack of sleep scores than subjects administered placebo.

Response to Treatment: For the active treatment (SCH 486757 and codeine) groups, subject global assessment of response to treatment was rated approximately 2 (mostly improved) on a 4-point scale at Day 5 or at treatment endpoint. For the placebo group, subject global assessment of response to treatment was rated ≥2 (mostly improved to some improvement). There was no difference between average scores in the SCH 486757- and codeine-treated groups. Both groups showed numerically better scores than the placebo group.

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 AUC(0-12 hr) values ranged from 211 to 4400 ng·hr/mL following twice-daily oral administration of SCH 486757 100 mg for 5 days. The intersubject variability in exposure obtained in this study was consistent with that observed in a previous study with robust sampling.

Safety: Overall, 37 (41%) of 91 subjects reported treatment-emergent adverse events. The incidence of treatment-emergent adverse events was comparable across treatments and appeared independent of sex. Ten (37.0%) of 27 subjects treated with SCH 486757 100 mg BID, 15 (44.1%) of 34 subjects treated with codeine 30 mg BID, and 12 (40%) of 30 subjects administered placebo reported treatment-emergent adverse events. Most treatment-emergent adverse events were mild to moderate.

The most common treatment-emergent adverse event in the SCH 486757-treated group was somnolence (n=7, 25.9% vs 8.8% in the codeine-treated group and 13.3% in the placebo group). All occurrences of somnolence were considered treatment related. Gastrointestinal disorders were the most common treatment-emergent adverse events reported by the codeine-treated group (n=10, 29.4% vs 14.8% in the SCH 486757-treated group and 13.3% in the placebo group). Most occurrences of gastrointestinal disorders in all treatment groups were considered treatment related.

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There were no deaths or other serious adverse events. Two subjects discontinued from the study because of adverse events: one each in the SCH 486757- and codeine-treated groups after 1 and 3 days of treatment, respectively.

No clinically significant changes in hematologic parameters, blood chemistry, urinalysis, or vital signs occurred in any treatment group. ECGs in two subjects in the SCH 486757-treated group showed abnormal PR intervals, but no clinically significant changes in QTcB occurred in any treatment group. The SCH 486757-treated group showed numerically greater increases in SSS scores than the other groups at the 0- to 4-hour and 0- to 8-hour time points on Days 1 and 5. The SSS findings confirm the higher incidence of somnolence reported as a treatment-emergent adverse event.

CONCLUSIONS:

- Subjects administered SCH 486757 100 mg BID showed some reduction from Baseline in average AM/PM cough severity score obtained from diary evaluations over Days 1 through 5, but the effect did not achieve statistical significance when compared with placebo.

- Subjects administered SCH 486757 100 mg BID showed a numeric reduction from Baseline in cough count measured by the LifeShirt system on both Days 1 and 5 when compared with placebo.

- Estimated AUC(0-12 hr) values ranged from 211 to 4400 ng·hr/mL following 5 days of dosing with SCH 486757 100 mg BID. The intersubject variability in exposure obtained in this study was consistent with that observed in a previous study with robust sampling.

- SCH 486757 was generally safe and well tolerated; however, a higher than expected incidence of somnolence was observed in 7 (25.9%) of 27 subjects in the active treatment group, a finding that was confirmed by the SSS scores. In comparison, somnolence was observed in 3 (8.8%) of 34 subjects in the codeine-treated group and in 4 (13.3%) of 30 subjects in the placebo group. Somnolence appears to be a common side effect of the drug when administered at the 100-mg BID dose.

Date of the Report: 29 FEB 2008