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 2, 12-Week, Double-Blind, Dose-Finding, Placebo-Controlled Study to Assess the Efficacy and Safety of a Range of SCH 420814 Doses (1 mg BID, 2 mg BID, 5 mg BID, and Possibly 10 mg BID) in Subjects With Moderate to Severe Parkinson's Disease Experiencing Motor Fluctuations and Dyskinesias (Protocol No. P04501)
Investigator(s): Multicenter	
Study Center(s): Multicenter study conducted in 44 sites in North America (United States, Canada), Latin America (Argentina, Chile, Colombia, Guatemala, Peru), Far East (Australia, New Zealand, Hong Kong, Singapore) and Europe (France, Italy, Spain, South Africa)	
Publication(s): None	
Studied Period: 04 DEC 2006 to 03 NOV 2008	**Clinical Phase:** 2
Objective(s): The primary objective of this study was to assess the efficacy of a range of preladenant doses (1 mg twice a day [BID], 2 mg BID, 5 mg BID, and 10 mg BID) in subjects with moderate to severe Parkinson's disease who were on a stable dose regimen of levodopa (L-dopa)/dopa decarboxylase inhibitor and other adjunctive treatments (ie, dopamine agonists, entacapone, or others) and were still experiencing "wearing off" or "sudden off" phenomena, motor fluctuations and dyskinesias. "Off" time is defined as when the subject's medication is not working and the Parkinson's disease symptoms are worse; "on" time is defined as when the medication is working and, therefore, these symptoms are better or absent. The secondary objective of this study was to assess the safety and tolerability of a range of preladenant doses (1 mg BID, 2 mg BID, 5 mg BID, and 10 mg BID).	
Methodology: This was a Phase 2, 12-week, multicenter, placebo-controlled, randomized, double-blind study of preladenant in subjects with moderate to severe idiopathic Parkinson's disease conducted in conformance with Good Clinical Practices (GCP). The study was designed as an adaptive clinical trial. The trial began with approximately 160 subjects to be randomized into four groups (n≅40 per group); preladenant dose groups of 1 mg BID, 2 mg BID and 5 mg BID and placebo. After 40 subjects completed the trial, the data regarding liver function were reviewed by an independent Drug Safety Monitoring Board (DSMB) looking for any evidence of hepatotoxicity. After review of the data, the DSMB advised that it was safe to add the 10 mg BID dose and a new preladenant dose group of 10 mg BID (n≅40) was added. The total sample size then increased to 200 subjects equally divided among five treatment arms. Visits occurred approximately every 2 weeks during the 12-week double-blind period: at Day 1 and Weeks 2, 4, 6, 8, 10, and 12 and at safety follow-ups.	
Number of Subjects: A total of 253 subjects received randomized treatment assignment and seven of these subjects did not receive study treatment. A total of 246 subjects were randomized and received at least one dose of study treatment; 199 subjects in the preladenant groups (49, 49, 47 and 54 in the preladenant 1 mg BID, 2 mg BID, 5 mg BID, and 10 mg BID groups, respectively) and 47 subjects in the placebo group. Demographic characteristics were similar among the treatment groups. The majority of subjects in all of the treatment groups were male (range, 59% to 73%) and white (range, 72% to 88%), with a mean age of approximately 62 years (range, 61.3 to 63.9 years). The majority of subjects had a Hoehn and Yahr staging of 2.5 or 3, and a mean mini-mental state examination score between 28.30 and 28.78.	
Diagnosis and Criteria for Inclusion: Subjects with a diagnosis of moderate to severe idiopathic Parkinson's disease for at least 5 years and on L-dopa for at least 2 years were included in this study. Subjects were permitted to take other Parkinson's disease medications such as dopamine agonists, dopa decarboxylase inhibitors, selegiline, Zydis selegiline, rasagiline, amantadine, coenzyme Q10, entacapone, and anticholinergics in addition to the L-dopa, provided that they had been on a stable regimen for at least 4 weeks before Screening. During the diary baseline period, subjects demonstrated a minimum of 2 hours of "off" time during awake time per day on 3 consecutive days.	
Test Product, Dose, Mode of Administration, Batch No(s): Preladenant was supplied as 1 mg (Batch Nos. [redacted] and 5 mg (Batch Nos. [redacted] oral capsules to be administered twice a day. Subjects assigned to preladenant 1 mg received one 1-mg capsule plus one placebo capsule BID, preladenant 2 mg received two 1-mg capsules BID, preladenant 5 mg received one 5-mg capsule plus one placebo capsule BID, and preladenant 10 mg received two 5-mg capsules BID.	

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Duration of Treatment: One to 2 week screening period, 1 week diary baseline period, 12 week treatment period and 6-week follow-up period.

Reference Therapy, Dose, Mode of Administration, Batch No(s): Subjects assigned to placebo received preladenant matching placebo (Batch Nos. [redacted] and [redacted] as two placebo capsules BID.

Criteria for Evaluation: Subjects were to have completed their daily diaries for at least 3 full days before their scheduled clinic visits. On the Subject Diary Card subjects were asked to choose among five options for each half-hour period: "off," "on" with no dyskinesias, "on" without troublesome dyskinesias, "on" with troublesome dyskinesias, or asleep.

The UPDRS is a frequently used multi-item scale which is designed to assess various aspects of the severity of Parkinson's disease. There are 42 items divided into 4 parts: Part 1 assesses mentation, Part II assesses activities of daily living (ADL), Part III assesses motor function and Part IV assesses complications of therapy. The complete UPDRS was to be performed at each visit except the Safety Follow-up visit. Subjects were not asked to be "on" when UPDRS was evaluated.

The primary efficacy endpoint was the mean change from Baseline to endpoint of 12 weeks of treatment in the 3-day average (based on subject diaries) of time in hours per day spent in the "off" state, over the 24-hour period. The secondary endpoints consisted of mean change from baseline:

- hours per day spent in the "off" state at each visit;
- hours awake per day spent in the "on" state at each visit and at endpoint;
- hours per day spent in the "on" state with no dyskinesias - at each visit and at endpoint;
- hours per day spent in the "on" state with troublesome dyskinesias - at each visit and at endpoint;
- hours per day spent in the "on" state without troublesome dyskinesias - at each visit and at endpoint;
- absolute duration of dyskinesias - at each visit and at endpoint;
- hours per day spent in total sleep time - at each visit and at endpoint;
- frequency of sleep attacks at each visit and at endpoint;
- UPDRS (Unified Parkinson's Disease Rating Scale) Score, Part I, Part II, Part III, and Part IV at each visit and at endpoint.

Safety assessments included adverse events (AEs), serious adverse events (SAEs), laboratory safety tests including liver function tests (LFTs), vital signs (pulse, blood pressure [BP], respiratory rate, temperature, and body weight), and electrocardiogram (ECG) parameters (atrial rate, ventricular rate, cardiac rhythm, PR interval, QRS duration, and QTc interval). At each visit, BP and pulse were to be measured prior to and 2 hours after the administration of study medication after the subject had been supine for 5 to 10 minutes and standing for 3 minutes

Statistical Methods: The baseline diary data were derived from the information collected in the 3-day daily diary card dispensed at Visit 2. The mean baseline values for diary parameters consisted of the mean number of hours per day using the 3-day values. At double-blind visits (Visits 3-9), the final 3 consecutive days of diary data for that visit were used to derive the mean number of hours per day for the diary parameters. These values were derived for each subject. If any subject had fewer than 3 consecutive days of diary data, the mean values were based on the average of the available number of days. The endpoint value was defined as the last 3 consecutive days available during the double-blind treatment period.

Comparisons of the various preladenant doses against placebo were performed in a sequential manner starting with the highest dose. A 2-sided alpha level of 0.049 was used to determine statistically significant differences. The overall alpha =0.05 was adjusted to 0.049 to account for the interim analysis.

The primary efficacy endpoint was evaluated using an analysis of covariance (ANCOVA) model with treatment effect and baseline covariates in the model.

Data for the secondary parameters were summarized and evaluated using the same ANCOVA model as the primary endpoint, with treatment effects and baseline covariates in the model. No statistical adjustments for multiplicity were planned for the secondary endpoints. A sensitivity analysis using analysis of variance (ANOVA) was performed on the primary endpoint.

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SUMMARY-CONCLUSIONS:

RESULTS:

Efficacy

- There was a statistically significant reduction in the primary endpoint, change from baseline to endpoint in the average hours spent per day in the "off" state, for both the preladenant 5 mg BID and 10 mg BID groups compared to the placebo group (LS mean difference of -1.0, p=0.049 and LS mean difference of -1.2, p=0.019, respectively).
- The least squares (LS) mean decrease from baseline to endpoint in the average hours spent per day in the "off" state showed a dose response, with a larger decrease with increasing preladenant dose (0.4, 1.3, 1.6, and 1.7 hours for the preladenant 1 mg BID, 2 mg BID, 5 mg BID, and 10 mg BID groups, respectively).
- The decrease in the average hours spent per day in the "off" state was larger in the preladenant 2 mg, 5 mg and 10 mg BID groups than in the placebo group starting at the 2 week visit, and this decrease was maintained throughout the trial. In addition to endpoint, there was a statistically significant reduction in the average hours spent per day in the "off" state for the preladenant 5 mg BID compared to the placebo group at Week 10 (LS mean difference -1.3, p=0.013) and Week 12 (LS mean difference -1.2, p=0.040), and for the preladenant 10 mg BID group vs placebo group at Week 8 (LS mean difference -1.2, p=0.034), Week 10 (LS mean difference -1.5, p=0.005) and Week 12 (LS mean difference -1.4, p=0.011).
- The difference in the LS mean increase in the average hours spent per day in the "on" state was statistically significant for the preladenant 5 mg BID and 10 mg BID groups compared with the placebo group from baseline to Week 10 (LS mean difference 1.4, p=0.012 and LS mean difference 1.2, p=0.025, respectively), Week 12 (LS mean difference 1.7, p=0.007 and LS mean difference 1.3, p=0.033, respectively), and endpoint (LS mean difference 1.2, p=0.024 and LS mean difference 1.1, p=0.049, respectively). The LS mean increase in the average hours spent per day in the "on" state was larger in the preladenant 2 mg, 5 mg and 10 mg BID groups than in the placebo group starting at the 2 week visit, and was maintained throughout the trial.
- There were statistically significant differences in the increase in the average hours per day spent in the "on" state without troublesome dyskinesias in the preladenant 2 mg BID and 10 mg BID groups vs the placebo group from baseline to endpoint (LS mean difference 1.2, p=0.025 and LS mean difference 1.1, p=0.047, respectively). There were no statistically significant differences in change from baseline to any visit in LS mean increase in the average hours per day spent in the "on" state with no dyskinesias or the "on" state with troublesome dyskinesias in the preladenant 1 mg BID, 2 mg BID, 5 mg BID or 10 mg BID groups vs the placebo group.
- There were no statistically significant differences at any visit or endpoint in the LS mean change between any of the preladenant dose groups compared with the placebo group in the proportion of time spent in the "on" state with no dyskinesias, with troublesome dyskinesias, without troublesome dyskinesias, and with any dyskinesia.
- There were no clinically meaningful changes during the study in the preladenant or placebo groups in mean total sleep time, sleep attacks, or the Epworth Sleepiness Scale.
- There was a statistically significant lowering of UPDRS part I for the preladenant 5 mg BID and 10 mg BID groups compared to the placebo group from baseline to endpoint (LS mean difference -0.8, p=0.004 and LS mean difference -0.6, p=0.040, respectively).
- The decreases in the LS mean UPDRS part II score at each visit were generally larger in the preladenant 5 mg BID (range, -1.0 to -2.7) and 10 mg BID (range, -0.3 to -1.8) groups, with smaller decreases in the preladenant 1 mg BID (range, 0.0 to -1.0), 2 mg BID (range, -0.4 to -1.3), and placebo (-0.2 to -1.0) groups.
- Although at endpoint there were no statistically significant differences between the preladenant groups and the placebo group for the UPDRS part III conducted at approximately 1 hour and 2 hours postdose, there was a dose response and trend toward increasing response among the preladenant groups.
- No statistically significant differences between the preladenant and placebo treatment groups were noted for the UPDRS part IV test.
- There were no statistically significant differences at any visit or endpoint in the LS mean change between any of the preladenant dose groups compared with the placebo group in total sleep time per day.

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- The pharmacokinetic analysis indicates that efficacy (reduction in "off" time) is a function of percent receptor occupancy and duration of occupancy, with model predicted threshold values for these two parameters of ≥50% and 9.8 hr, respectively. The preladenant 5 mg BID and the 10 mg BID groups met both of these criteria.

Safety:

- The percentage of subjects reporting AEs was similar among the 1 mg BID, 2 mg BID, 5 mg BID and 10 mg BID preladenant groups (82%, 80%, 85% and 87%, respectively), and slightly smaller in the placebo group (74%). AEs reported by at least 10% of subjects in any of the preladenant groups included constipation, nausea, dizziness, headache, Parkinson's disease, dyskinesia, and somnolence.
- The percentage of subjects reporting treatment related AEs in the preladenant 1 mg BID, 2 mg BID, 5 mg BID and 10 mg BID groups, and the placebo group was 61%, 49%, 62%, 65%, and 47%, respectively. Treatment related AEs reported by at least 10% of subjects in any of the preladenant groups included constipation, nausea, Parkinson's disease, dyskinesia, and somnolence.
- The percentage of subjects reporting severe or life-threatening AEs in the preladenant 1 mg BID, 2 mg BID, 5 mg BID and 10 mg BID groups and placebo group was 8%, 2%, 4%, 17% and 9%, respectively. In the majority of the subjects the AEs were severe (6%, 2%, 4%, 15% and 9% in the preladenant 1 mg BID, 2 mg BID, 5 mg BID and 10 mg BID groups and placebo group, respectively), with only two subjects in the preladenant groups reporting AEs which were assessed by the investigator to be of life-threatening severity: angina pectoris in the preladenant 10 mg BID group and intestinal obstruction in the preladenant 1 mg BID group. These events were also reported as SAEs. More subjects in the preladenant 10 mg BID group reported severe AEs.
- One subject died from an MI during the screening phase shortly after signing the informed consent. This subject was not randomized and did not receive study drug. No deaths occurred in any randomized subject during the study. The percentage of subjects reporting SAEs was small and similar among the preladenant 1 mg BID, 2 mg BID, 5 mg BID and 10 mg BID groups and the placebo group with an onset during the treatment phase (4%, 2%, 0, 4%, and 2%, respectively) or follow-up phase (6%, 2%, 2%, 6%, and 6%, respectively), showing no trend towards a dose response.
- The percentage of subjects reporting AEs that led to discontinuation in the preladenant 1 mg BID, 2 mg BID, 5 mg BID and 10 mg BID groups and the placebo group was 24%, 4%, 11%, 19%, and 13%, respectively. More subjects had AEs that led to discontinuation in the preladenant 1 mg BID and 10 mg BID groups. The most commonly reported AE that led to discontinuation was dyskinesia.
- None of the subjects in the preladenant groups with baseline values and on-treatment laboratory results experienced either ALT elevations ≥3 X ULN or had total bilirubin (T-BIL) elevations ≥2 X ULN. One subject in the placebo group had an AST ≥ 3 X ULN. None of the preladenant study group subjects and none of the placebo group subjects in this study fulfilled Hy's Law (ALT and/or AST >3X ULN and associated with an increase in bilirubin ≥2X ULN).
- Small, non-dose-dependent elevations in BP were observed in all preladenant treatment groups relative to placebo following the first dose of study medication. Compared to Day 1 baseline, preladenant-treated subjects experienced an average systolic blood pressure (SBP) increase of 2.8 to 6.7 mm Hg and diastolic blood pressure (DBP) increase of 0.5 to 2 mm Hg at the Day 1 post-dose measurement. At subsequent visits, SBP returned to baseline levels. Placebo-treated subjects, however, experienced a decline in SBP at the Day 1 post-dose measurement with a trend toward continuing decline throughout the treatment and follow-up periods. Overall, the study population was normotensive at baseline and remained normotensive throughout the study, despite the observed BP changes between preladenant and placebo treatment groups.

CONCLUSIONS

The following conclusions can be drawn from this study:

- There was a statistically significant reduction in the primary endpoint, change from baseline to end of treatment in the average hours spent per day in the "off" state, for both the preladenant 5 mg BID and 10 mg BID groups compared to the placebo group (LS mean difference of -1.0, p=0.049 and LS mean difference of -1.2, p=0.019, respectively). The LS mean decrease from baseline to endpoint in the average hours spent per day in the "off" state showed a dose response, with a larger decrease with increasing preladenant dose.

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- The LS mean increase in the average hours spent per day in the "on" state was larger in the preladenant 2 mg, 5 mg and 10 mg BID groups than in the placebo group starting at the 2 week visit, and was maintained throughout the trial, with statistically significant differences for the preladenant 5 mg BID and 10 mg BID groups compared with the placebo group from baseline to endpoint (LS mean difference 1.2, p=0.024 and LS mean difference 1.1, p=0.049, respectively).
- There were statistically significant increases in the average hours per day spent in the "on" state without troublesome dyskinesias in the preladenant 2 mg BID and 10 mg BID groups vs the placebo group from baseline to endpoint (LS mean difference 1.2, p=0.025 and LS mean difference 1.1, p=0.047, respectively).
- There were no clinically meaningful changes during the study in the preladenant or placebo groups in mean total sleep time, sleep attacks, or the Epworth Sleepiness Scale.
- There was a statistically significant lowering of UPDRS part I for the preladenant 5 mg BID and 10 mg BID groups compared to the placebo group from baseline to endpoint (LS mean difference -0.8, p=0.004 and LS mean difference -0.6, p=0.040, respectively).
- The decreases in the LS mean UPDRS part II score at each visit were generally larger in the preladenant 5 mg BID and 10 mg BID groups, with smaller decreases in the preladenant 1 mg BID, 2 mg BID, and placebo groups.
- Although at endpoint there were no statistically significant differences between the preladenant groups and the placebo group for the UPDRS part III conducted at approximately 1 hour and 2 hours postdose, there was a dose response and trend toward increasing response among the preladenant groups.
- Preladenant was generally well tolerated in this study.
- One subject died from a myocardial infarction (MI) during the screening phase shortly after signing the informed consent. This subject was not randomized and did not receive study drug. No deaths occurred in any randomized subject during the study. The percentage of subjects reporting SAEs was small and similar among the preladenant 1 mg BID, 2 mg BID, 5 mg BID and 10 mg BID groups and the placebo group, showing no trend towards a dose response.
- None of the subjects in the preladenant groups with baseline values and on-treatment laboratory results experienced either ALT elevations ≥3 X ULN or had total bilirubin elevations ≥2 X ULN. One subject in the placebo group had an AST ≥ 3 X ULN. None of the preladenant study group subjects and none of the placebo group subjects in this study fulfilled Hy's Law (ALT and/or AST >3X ULN and associated with an increase in bilirubin ≥2X ULN).
- There were differences in BP changes in the preladenant groups compared to the placebo group, predominantly related to SBP postdose. These differences in SBP changes were small and averaged in the magnitude of 2 to 6 mm Hg. Overall, the study population was normotensive at baseline and remained normotensive throughout the study, despite the observed BP changes between preladenant and placebo treatment groups.

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