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2 SYNOPSIS

Title of Trial:	A PHASE 2, 36-WEEK, OPEN-LABEL, UNCONTROLLED SAFETY FOLLOW-UP STUDY ASSESSING SCH 420814 (PRELADENANT) 5 MG BID (P05175**)**
Investigator(s): Multicenter	
Trial Center(s): Multicenter study conducted in 38 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, Spain)	
Publication(s): None	
Studied Period: 05 DEC 2007 to 27 OCT 2009	**Clinical Phase:** 2
Objective(s): The primary objective of this trial was to assess the long-term safety of a 5 mg twice a day (BID) dose of preladenant. The secondary objective of this trial was to assess the long-term efficacy of a 5 mg BID dose of preladenant.	
Methodology: This was a Phase 2, 36-week, multicenter, open-label, uncontrolled trial of preladenant 5 mg BID in subjects with moderate to severe idiopathic Parkinson's Disease conducted in conformance with Good Clinical Practices. A subject could enter trial P05175 from trial P04501 if the subject either had completed trial P04501, or if the subject was discontinued from trial P04501 for reasons other than a serious adverse event (SAE) or elevated liver function test (LFT) results. The trial consisted of a 36-week Treatment Period followed by a 6-week Follow-up Period.	
Number of Subjects: Up to approximately 200 subjects were planned. A total of 142 subjects were screened and 140 subjects were enrolled and treated (two subjects did not meet eligibility requirements).	
Diagnosis and Criteria for Inclusion: Subjects must have completed trial P04501 or discontinued for reasons other than SAEs or elevated LFT results. Subjects who had 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.	
Test Product, Dose, Mode of Administration, Batch No(s): Preladenant was supplied as 5 mg (Batch Nos. [redacted] oral capsules to be administered BID.	
Duration of Treatment: 1-week screening period, 36-week treatment period, and 6-week follow-up period	
Reference Therapy, Dose, Mode of Administration, Batch No(s): Not applicable	
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 primary endpoint for the trial was assessment of the proportion of subjects reporting adverse events (AEs) during the 36 weeks of open-label treatment. The following efficacy endpoints were reported: • hours per day spent in the "off" state at each visit; • hours awake per day spent in the "on" state; • hours per day spent in the "on" state with no dyskinesias; • hours per day spent in the "on" state with troublesome dyskinesias; • hours per day spent in the "on" state without troublesome dyskinesias; • absolute duration of dyskinesias; • hours per day spent in total sleep time Safety assessments included AEs, SAEs, laboratory safety tests including 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).	
Statistical Methods: All subjects enrolled in the long-term follow-up trial were included in the subject listings and tabulations. Data collected during the trial were listed for medical review; no inferential statistics were applied. The number of	

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subjects reporting any AE, the incidence of specific AEs, and discontinuations due to AEs were tabulated. Laboratory data were listed and summarized; values outside the normal ranges were flagged. Vital signs were listed and summarized.

SUMMARY-CONCLUSIONS:

RESULTS:

Disposition and Demographics: A total of 142 subjects were screened and 140 subjects enrolled. Of the 140 subjects enrolled, 106 subjects (76%) completed the treatment phase and 34 subjects (24%) did not complete the treatment phase. Reasons for not completing the treatment phase included AE in 19 subjects (14%), subject did not wish to continue for reasons unrelated to assigned trial treatment in 13 subjects (9%), and non-compliance with protocol in 2 subjects (1%). A total of 135 subjects entered and 126 subjects (93%) completed the follow-up phase. Reasons for not completing the follow-up phase included subject did not wish to continue for reasons unrelated to assigned trial treatment in 6 subjects (4%), and subject withdrew consent in 3 subjects (2%).

A total of 95 subjects (68%) were male, 105 subjects (75%) were white, and the mean age of the total population was 62.9 years.

The mean (median) duration of treatment with preladenant was 31 (36) weeks.

Efficacy: No baseline data were collected for the subject diaries in trial P05175, therefore, changes from baseline were calculated two ways; one with baseline defined as the baseline of the double-blind trial P04501 and the other with the baseline defined as the last assessment of P04501. It should be noted that due to the planned 6-week safety follow-up in P04501 and the delay some subjects experienced between completing P04501 and enrolling in P05175, a median treatment gap for preladenant of 119 days occurred. During this time, subjects continued to receive their other medications for Parkinson's Disease.

The decrease from baseline in average "off" time values ranged from -1.4 to -1.9 hours/day over Weeks 4 to 36 in trial P05175 compared to -1.3 hours/day at the end of P04501. The increases from baseline in average "on" time values ranged from 1.2 to 1.5 hours/day over Weeks 4 to 36 in trial P05175 compared to 1.0 hours/day at the end of trial P04501. Compared to the P04501 baseline value, at the end of trial P05175, subjects reported similar proportions of "on" time without troublesome dyskinesia, higher proportions of "on" time with troublesome dyskinesia, and lower proportions of "on" time with no dyskinesia.

Safety: A total of 123 subjects (88%) reported treatment-emergent AEs. AEs reported by at least 10% of subjects were dyskinesia (33%), constipation (19%), Parkinson's Disease (14%), fall (13%), somnolence (11%), and back pain (10%).

A total of 91 subjects (65%) reported treatment-emergent treatment-related AEs. Treatment-emergent, treatment-related AEs reported by at least 10% of subjects were dyskinesia (28%) and constipation (10%).

Two subjects died during this trial. Both deaths were assessed by the investigator as unrelated to trial drug.

[redacted]

A total of 24 subjects (17%) reported SAEs during the trial; 18 subjects (13%) reported SAEs with an onset during the treatment phase, 6 subjects (4 %) reported SAEs with an onset during the follow-up phase, and one subject who did not enter the follow-up phase reported an SAE within 30 days of the end of treatment. Of the 24 subjects, one subject reported an SAE during both the treatment and follow-up phase. SAEs reported by more than one subject during the entire trial were dyskinesia, myocardial infarction, Parkinson's Disease, and transient ischemic attack in two subjects (1%) each.

A total of 19 subjects (14%) experienced AEs that led to discontinuation. The only AEs that led to the discontinuation of more than one subject were Parkinson's Disease and insomnia (two subjects each).

None of the subjects in this study fulfilled Hy's Law (ALT and/or AST >3X ULN and associated with an increase in bilirubin ≥2X ULN).

No overall trends in BP over time were noted.

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CONCLUSIONS:

The following conclusions can be drawn from this long-term trial:

- Preladenant was generally well tolerated in this trial.
- A total of 24 subjects (17%) reported SAEs during the trial. Two subjects died during this trial and both deaths were assessed by the investigator as unrelated to trial drug.
- None of the subjects in this study fulfilled Hy's Law (ALT and/or AST >3X ULN and associated with an increase in bilirubin ≥2X ULN).
- No overall trends in BP over time were noted.
- The decrease from baseline in average "off" time values ranged from -1.4 to -1.9 hours/day in trial P05175 compared to -1.3 hours/day at the end of P04501.
- The increases from baseline in average "on" time values ranged from 1.2 to 1.5 hours/day in trial P05175 compared to 1.0 hours/day at the end of trial P04501.
- Compared to the P04501 baseline value, at the end of trial P05175, subjects reported similar proportions of "on" time without troublesome dyskinesia, higher proportions of "on" time with troublesome dyskinesia, and lower proportions of "on" time with no dyskinesia.

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