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.

2.0 SYNOPSIS

MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC.
MK-3814 (SCH 420814)
Preladenant, tablet
Adenosine 2a receptor antagonist

CLINICAL STUDY REPORT SYNOPSIS

PROTOCOL TITLE/NO.: A Phase 3, 12-Week, Double-Blind, Double-Dummy, Placebo- and Active-Controlled Efficacy and Safety Study of Preladenant in Subjects With Moderate to Severe Parkinson's Disease (PD) / Protocol No. P04938

INVESTIGATORS/STUDY CENTERS: Multicenter study (121 sites randomized subjects) in Asia (India), Eastern Europe (Bulgaria, Czech Republic, Poland, Russia, and Turkey), Europe (Austria, Finland, France, Germany, Israel, Italy, Netherlands, Portugal, Spain, Sweden, and United Kingdom), North America (Canada and United States), and South America (Brazil and Peru).

PUBLICATIONS: None

PRIMARY THERAPY PERIOD:	**CLINICAL PHASE:** 3
15 JUL 2010 to 20 DEC 2012	

DURATION OF TREATMENT: Up to 5 weeks of screening. 12 week treatment period. At the end of treatment, the subject could choose to enroll in an extension trial (up until approximately the maximum number of subjects for the extension trial has been reached) or return for a follow-up visit 2 weeks after the last dose of study drug.

OBJECTIVES:

Primary Efficacy Objective:

To evaluate the efficacy of a range of preladenant doses compared with placebo in subjects with moderate to severe PD experiencing motor fluctuations and receiving a stable dose of levodopa (L-dopa), as measured by "off" time.

Primary Safety Objective:

To assess the safety and tolerability of preladenant compared with placebo in subjects with moderate to severe PD experiencing motor fluctuations and receiving a stable dose of L-dopa.

Key Secondary Trial Objective:

To evaluate the efficacy of a range of preladenant doses compared with placebo in subjects with moderate to severe PD experiencing motor fluctuations and receiving a stable dose of L-dopa as measured by the proportion of Responders and by "on" time without troublesome dyskinesia.

STUDY DESIGN: This trial was a randomized, placebo- and active-controlled, dose-range-finding, parallel-group, multi-center, double-blind trial of preladenant in adult subjects with moderate to severe PD that was conducted in conformance with Good Clinical Practice. Subjects were randomized into one of five treatment groups (preladenant 2 mg, 5 mg, or 10 mg twice daily [BID] or placebo or rasagiline 1 mg once daily [QD]) in a 1:1:1:1:1 ratio and received double-blind treatment for 12 weeks. At the End of Treatment, the subject could choose to enroll in an extension trial (up until approximately the maximum number of subjects for the extension trial has been reached) or return for a Follow-up Visit 2 weeks after the last dose of study drug.

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SUBJECT/PATIENT DISPOSITION: Of the 1076 enrolled, a total of 778 subjects were given randomized treatment assignments with 156 subjects in the preladenant 2 mg BID treatment group, 155 subjects in the 5 mg BID treatment group, 156 subjects in the 10 mg BID treatment group, 156 subjects in the rasagiline treatment group, and 155 subjects in the placebo treatment group.

DOSAGE/FORMULATION NUMBERS: Preladenant was supplied as an oral tablet to be administered BID. Rasagiline was supplied as a capsule. Placebo tablets matching preladenant and placebo capsules matching rasagiline were also provided. During the 12-week Treatment Period, subjects received one tablet and one capsule orally each morning and one tablet orally each evening in a double-blind, double-dummy design.

DIAGNOSIS/INCLUSION CRITERIA:

Adult subjects with a diagnosis of moderate to severe idiopathic PD were selected to participate in the trial based on the following.

Inclusion Criteria: The subject must fulfill all the criteria listed below for entry.

- Each subject must have a diagnosis of idiopathic PD based on the United Kingdom Parkinson's Disease Society Brain Bank Criteria and the inclusion/exclusion criteria for this protocol.
- Each subject should have bradykinesia and at least one of the following symptoms:
  - Muscular rigidity
  - Resting tremor (4 Hz to 6 Hz; Please note that for the purposes of this study, a diagnosis based solely on bradykinesia and postural instability is insufficient for diagnosis of idiopathic PD, and subjects diagnosed in this manner cannot be enrolled in the study).
- Each subject must have received prior therapy with L-dopa for approximately 1 or more years immediately before Screening and must continue to have a beneficial clinical response to L-dopa at Screening.
- Each subject must have been on a stable, optimal dopaminergic treatment regimen, defined as maximum therapeutic effect achieved with available anti-parkinsonian treatment, for at least the 5 weeks immediately before Randomization.
- Subjects receiving one or more of the adjunct PD medications listed in the allowed medications table were permitted to enroll in the trial. Each subject who was receiving one or more of the adjunct PD medications listed below must have been on a stable regimen of treatment for at least the 4 weeks immediately before Randomization.

Allowed Medications Table
Amantadine
Anticholinergics
Dopa decarboxylase inhibitors
Dopamine agonists
Entacapone
L-dopa

- Each subject's Hoehn and Yahr stage must be ≥ 2.5 and ≤ 4 in the optimum "on" state at Screening.
- Each subject must be experiencing motor fluctuations with or without dyskinesia following optimum titration of treatment medications and within the 5 weeks immediately before Screening.
- Each subject must be experiencing a minimum of 2 hours/day of "off" time as estimated by the investigator and supported by the 3-day symptom diary (Daily Diary) at Randomization.
- Each subject, with or without the help of a caregiver, must be capable of maintaining an accurate and complete symptom Daily Diary as assessed at the Diary Training Visit.
- Each subject (or subject's legal representative) must be willing and able to provide written informed consent for the trial. For a subject who is unable to provide independent consent, a legal representative may provide written informed consent. Subjects who are unwilling to provide written informed consent for exploratory pharmacogenetic testing may be included in the trial; however, exploratory pharmacogenetic samples must not be obtained.
- Each subject must be ≥30 to ≤85 years of age. A subject may be of either sex, any race/ethnicity.
- Each subject must have results of Screening clinical laboratory tests (hematology, blood chemistries, and urinalysis) drawn within 5 weeks prior to Randomization, clinically acceptable to the investigator, and not within the parameters specified for exclusion.
- Each subject must have results of a physical examination within normal limits or clinically acceptable limits to the investigator.
- Each subject must be able to adhere to dose and visit schedules.
- All subjects that are sexually active or plan to be sexually active agree to use a highly effective method of birth control while the subject is in the study and for 2 weeks after the last dose of study drug. A male subject must also not donate sperm during the trial and within 2 weeks after the last dose of study drug. Complete details regarding contraceptive requirements are specified in Section 7.7.2.7 of the protocol located in **Section 16.1.1**.

Exclusion Criteria: Subjects were not entered into the study if they violated any of the exclusion criteria listed below.

Exclusion Criteria Related to PD (Neurologic and Psychiatric):

- A subject must not have a form of drug-induced or atypical parkinsonism, cognitive impairment (i.e., MoCA score <22), bipolar disorder, schizophrenia, or other psychotic disorder. (Subjects with non-troublesome hallucinations, stable on low dose quetiapine or clozapine are allowed to enroll.)
- A subject must not have a history of any of the following:
  - repeated strokes with stepwise progression of Parkinsonian features
  - repeated head injury
  - definitive encephalitis
  - oculogyric crises

- neuroleptic treatment at onset of symptoms
- more than one first degree relative affected
- sustained remission
- strictly unilateral features after 3 years
- supranuclear gaze palsy
- cerebellar signs
- early severe autonomic involvement
- severe symptomatic autonomic involvement unrelated to medications
- early severe dementia with disturbances of memory, language, and praxis
- Babinski sign with clear, clinically significant pyramidal tract involvement
- presence of cerebral tumor or communicating hydrocephalus on neuroimaging (by history)
- negative response to large doses of L-dopa (if malabsorption excluded)
- (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)or known neurotoxin exposure
- hallucinations unrelated to medications
- stroke within 6 months of Screening or persistent neurological deficit that may interfere with study assessments
- surgery for PD

- A subject must not have an untreated major depressive disorder meeting Diagnostic and Statistical Manual of Mental Disorders IV Text Revision (DSM-IV-TR) criteria or Beck Depression Inventory II] {BDI II} score ≥19. A subject who is successfully treated [Beck Depression Inventory-II] {BDI-II} score <19] with stable doses of allowed antidepressant medications for at least the 5 weeks immediately before Screening is eligible to enroll in the trial.)

- A subject must not be at imminent risk of self-harm or harm to others, in the investigator's opinion based on clinical interview and responses provided on the Columbia-Suicide Severity Rating Scale (C-SSRS). Subjects must be excluded if they report suicidal ideation of Type 4 or 5 in the past 2 months or suicidal behavior in the past 6 months as measured by the C-SSRS during Screening or since Screening or Randomization Visits.

- In the judgment of the investigator, a subject must not have sleep attacks or compulsive behavior that would interfere with the integrity of the trial or would pose a risk to the subject in participating in the trial.

Other Exclusion Criteria:

- **Blood Pressure:** A subject must not have a systolic blood pressure (BP) ≥150 mm Hg OR diastolic BP ≥95 mm Hg at Screening and at a BP recheck prior to Randomization. Should the BP remain elevated, the subject may not enter the trial until the BP has been adequately controlled with antihypertensive medication as demonstrated by 2 BP measurements meeting this criterion at consecutive separate visits (scheduled or unscheduled) within 5 weeks prior to Randomization. If antihypertensive medications are used to control a subject's BP, the subject's BP and doses of antihypertensive medications must be stable for at least 2 weeks prior to randomization. Note: During the course of the study,

antihypertensive medication maybe initiated or increased to control a subject's BP at any time during treatment in P04938 as needed.

- **Cardiovascular Disease:** A subject must not have had any clinically significant cardiovascular event or procedure for 6 months prior to Randomization, including, but not limited to, myocardial infarction, prolonged QTc interval [a subject must not have a QTc result > 500 msec], angioplasty, unstable angina, or heart failure; and a subject must not have heart failure staged New York Heart Association Class III or IV.

- **Liver Enzymes:** A subject must not have an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥3 x upper limit of normal (ULN) or total bilirubin (T-BIL) ≥1.5 x ULN. Should an LFT be abnormal (ALT/AST >ULN but <3 x ULN, T-BIL >ULN but <1.5 x ULN) at Screening, the investigator should attempt to characterize at entry the reason(s) for elevation(s), e.g., alcohol abuse (see next exclusion criterion), metabolic syndrome with fatty liver, etc. No repeat testing is allowed. Subjects with suspected Gilbert's Syndrome who have isolated T-BILI ≥ 1.5 x ULN may enter the study upon genetic confirmation (UGT1A1 assessment).

- **Liver Disease:** A subject must not have active serologically confirmed hepatic dysfunction (defined as viral infection [Hepatitis B, C, or E; Epstein-Barr virus (EBV); cytomegalovirus {CMV}]) or a history of diagnosis of drug- or alcohol-induced hepatic toxicity or frank hepatitis. If a subject has abnormal ALT or AST at Screening (>1.5 x ULN), the subject must have serology testing to rule out active viral hepatitis. A subject who has a history of serologically confirmed EBV or CMV may be enrolled in the trial as long as his/her viral infection was not associated with hepatitis in the past, and his/her ALT and AST are normal at Screening. Types of serology assays to be performed are specified in the table of Laboratory Tests in the protocol [**16.1.1**].

- A subject must not have a history within the past 5 years of a primary or recurrent malignant disease with the exception of adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or in situ prostate cancer with a normal prostate-specific antigen (PSA) post resection.

- **Prohibited Concomitant Medications:** A subject must not have received any treatment listed in the prohibited medications table more recently than the indicated period before Randomization.

- A subject must not need to continue to receive any treatment listed in the prohibited medications table during the trial.

  Note: Warnings and Contraindications detailed in the Prescribing Information for the medications listed in allowed medications table should be followed.

Prohibited Medications, Supplements, and Other Substances for Entry into the Trial

Protocol No. P04938

Prohibited Medications, Supplements, and Other Substances for Entry into the Trial	Period Before Randomization
Tolcapone	4 weeks
Irreversible monoamine oxidase (MAO) inhibitors, e.g., rasagiline, selegiline, Zydis selegiline	4 weeks

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Reversible MAOB or MAOA inhibitor	4 weeks
Centrally acting dopamine antagonist (including metoclopramide, sulpiride, Tiapride etc.)	4 weeks
α-methyldopa	4 weeks
Methylphenidate	4 weeks
Reserpine	4 weeks
Amphetamines	4 weeks
Flunarizine	4 weeks
Cinnarizine	4 weeks
Theophylline	4 weeks
Diphenhydramine used to treat parkinsonism	4 weeks
Meperidine, tramadol, methadone, propoxyphene, cocaine, or local anesthesia containing sympathomimetic vasoconstrictors	2 weeks
Dextromethorphan	2 weeks
Mirtazapine (a tetracyclic antidepressant), and cyclobenzaprine (a tricyclic muscle relaxant)	2 weeks
Sympathomimetic amines including cold products, nasal and oral decongestants, and weight-reducing preparations that contain vasoconstrictors (e.g., ephedrine, pseudoephedrine, phenylephrine, and phenylpropanolamine)	2 weeks
St. John's wort, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, and selective serotonin reuptake inhibitors with the following exceptions: citalopram $\leq$20 mg/day, escitalopram $\leq$20 mg/day, paroxetine $\leq$30 mg/day, amitriptyline or nortriptyline $\leq$50 mg/day, trazodone or sertraline $\leq$100 mg/day	5 weeks
High tyramine-containing aged cheeses (e.g., Stilton)	2 weeks
Other potentially hepatotoxic drugs (including amiodarone, azathioprine, felbamate, imatinib, isoniazid, isotretinoin, leflunomide, methotrexate, nevirapine, pioglitazone, rosiglitazone, pyrazinamide, valproic acid, and voriconazole)	4 weeks
Potent CYP3A4 inhibitors (e.g., ritonavir, nelfinavir, indinavir); macrolide antibiotics (e.g., erythromycin, clarithromycin, troleandomycin, telithromycin, [azithromycin is allowed]); and systemically administered antifungal agents (e.g., ketoconazole, itraconazole)	4 weeks
CYP3A4 inducers (e.g., phenytoin, phenobarbital, barbiturates, systemic glucocorticoids)	4 weeks
Atypical and typical neuroleptics (including depot formulations) except low dose quetiapine fumarate and clozapine	6 months

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- A subject must not have an average daily consumption of more than three 4-ounce glasses (118 mL) of wine or the equivalent.
- A subject must not have poorly controlled diabetes (e.g., HbA1c >8.5) or significantly abnormal renal function (e.g., creatinine >2.0 mg/dL) in the opinion of the investigator.
- A subject must not have a severe or ongoing unstable medical condition (e.g., any form of clinically significant cardiac disease, symptomatic orthostatic hypotension, seizures, or alcohol/drug dependence).
- A subject must not have participated in any studies using preladenant.
- A subject must not have allergy/sensitivity to the investigational products or their excipients.
- A female subject must not be breast-feeding or considering breast-feeding.
- A female subject must not be pregnant or intending to become pregnant.
- A subject must not have any clinically significant condition or situation, other than the condition being studied that, in the opinion of the investigator, would interfere with the trial evaluations or optimal participation in the trial.
- A subject must not have used any investigational drugs within 90 days immediately before Screening.
- A subject must not have been participating in any other clinical trial within 90 days, inclusive, of signing the informed consent form of this trial.
- A subject must not be a member or a family member of the personnel of the investigational or sponsor staff directly involved with this trial.

EVALUATION CRITERIA:

Subjects were to have completed their daily diaries for at least 3 full days immediately before their scheduled clinic visits during the double-blind treatment period

The primary efficacy endpoint was the change from Baseline to End of treatment (Week 12) in mean “off” time in hours per day.

The key secondary efficacy endpoints were:

- The proportion of Responders, where Responder is defined as a subject with at least a 30% reduction in mean “off” time from Baseline to End of Treatment (Week 12).
- The change from Baseline to End of Treatment (Week 12) in mean “on” time without troublesome dyskinesias in hours per day.

Other efficacy endpoints for this trial were:

- Diary data which include:
  - Mean hours per day spent in the “off” state at Weeks 2, 4 and 8.
  - Mean hours per day spent in the “on” state at Weeks 2, 4, 8, and 12.
  - Mean hours per day spent in the “on” state without troublesome dyskinesia at Weeks 2, 4 and 8.
  - Mean hours per day spent in the “on” state with troublesome dyskinesia at Weeks 2, 4,

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8, and 12.

- Proportion of “on” time with no dyskinesias at Weeks 2, 4, 8, and 12.
- Proportion of “on” time without troublesome dyskinesias at Weeks 2, 4, 8, and 12.
- Proportion of “on” time with troublesome dyskinesias at Weeks 2, 4, 8, and 12.
- Mean total sleep time at Weeks 2, 4, 8, and 12.

- UPDRS data which include
  - Total UPDRS score in the “on” state.
  - UPDRS score for Parts 1, 2, and 3 combined.
  - UPDRS score for Parts 2 and 3 combined.
  - UPDRS subscale scores for Parts 1, 2, 3, and 4.
  - Tremor domain of the UPDRS Part 3.
- MoCA score.
- EQ 5D score.
- PDQ 39 score.
- BDI II score.
- Apathy score.

Prespecified safety endpoints (Tier 1 events) were defined as the incidences of:

- Systolic BP (SBP) ≥ 180 mm Hg
- Diastolic BP (DBP) ≥ 105 mm Hg
- ALT ≥ 3 X ULN and ≥ 10% increase from Baseline
- AST ≥ 3 X ULN and ≥ 10% increase from Baseline
- Suicidality
- Epworth Sleepiness Scale score

The commonly occurring safety endpoints included the AE preferred terms not included in the prespecified safety endpoints, but observed to be “common.” For this trial, an AE was considered “common” if it occurred in ≥ 4 subjects in any treatment group (Tier 2 events).

Descriptive Endpoints included all other AE preferred terms plus laboratory assessments, electrocardiogram (ECG)s, vital signs, QUIP-RS score, Suicidal Behavior, Suicidal Ideation, Sleep Attack Questionnaire results, etc, not analyzed in the prespecified safety endpoints or identified among the commonly occurring safety endpoints.

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STATISTICAL PLANNING AND ANALYSIS:

Data Sets to be Analyzed

Full Analysis Set (FAS): All randomized subjects with subjects excluded for the following reasons: failure to receive at least one dose of study treatment; lack of any post-Randomization endpoint data subsequent to at least one dose of study treatment; and lack of Baseline data for those analyses requiring Baseline data. Efficacy analyses were conducted using the FAS. Randomization was preserved in the efficacy analyses. Safety analyses were conducted using the all subjects as treated (ASaT) Set. In the safety analyses, subjects were analyzed according to the treatment actually received.

ASaT Set: All subjects who received at least one dose of study drug.

Sample Size: A one-hour decrease in average "off" time is considered to be clinically meaningful. The total target sample size in this study was 750 subjects or 150 subjects per treatment group which would provide at least 90% power to detect a difference between preladenant and placebo of 1 hour in change from Baseline to Week 12 in mean “off” time given a standard deviation of 2.6 hours and a two-sided alpha = 0.05. The 2.6 hour standard deviation was derived from the phase 2 study, P04501.

Primary Efficacy Analysis

Hypothesis 1 (Primary Hypothesis): At least the 10 mg BID dose of preladenant is superior to placebo as measured by the change from Baseline to Week 12 in the mean “off” time.

The Primary Efficacy Endpoint for this trial was the change from Baseline to End of Treatment (Week 12) in mean “off” time in hours per day (Diary). The primary efficacy endpoint was analyzed using a constrained longitudinal data analysis (cLDA) approach with treatment, time, treatment-by-time interaction, and subject effects in the model. The least squares mean (LSM) response and pairwise differences among preladenant doses and placebo along with 95% confidence intervals have been provided. P-values from tests of preladenant versus placebo for this endpoint constitute tests of the Primary Hypothesis. Using the same model, a comparison of the rasagiline response versus placebo also was done for the Primary Efficacy Endpoint. The Least squares mean (LSM), pairwise difference, and 95% confidence intervals have been provided. In addition, 95% confidence intervals comparing each preladenant dose to rasagiline have been tabulated. An analysis of covariance (ANCOVA) with treatment effect and Baseline covariate was conducted as a sensitivity analysis for the last-observation-carried-forward (LOCF) data for the Primary Endpoint.

Key Secondary Efficacy Analysis: There are two Key Secondary Hypotheses:

Hypothesis 2: At least the 10 mg BID dose of preladenant is superior to placebo as measured by the proportion of subjects with at least a 30% reduction in mean "off" time from Baseline to Week 12.

Hypothesis 3: At least the 10 mg BID dose of preladenant is superior to placebo as measured by the change from Baseline to Week 12 in mean "on" time without troublesome dyskinesia.

The Key Secondary Efficacy Endpoints were:

- The proportion of Responders, where a Responder is defined as a subject with at least a 30% reduction in mean "off" time from Baseline to Week 12.
- The change from Baseline to Week 12 in mean "on" time without troublesome dyskinesia in hours per day.

The proportion of Responders was analyzed using a generalized linear mixed model with

treatment effect and Baseline mean "off" time as a covariate. Responder rates for each treatment arm are presented along with odds ratios and 95% confidence intervals for the odds ratios comparing preladenant dose groups with placebo. The change from Baseline in the mean "on" time without troublesome dyskinesias was evaluated using the same cLDA model used for the Primary Endpoint. The LSM and pairwise differences between preladenant doses and placebo along with 95% confidence intervals have been provided. P-values from tests of preladenant versus placebo for these endpoints constitute tests of the Key Secondary Hypotheses.

Using the same models, a comparison of the rasagiline response versus placebo also was done for the Key Secondary Efficacy parameters. For the change from Baseline in the mean "on" time without troublesome dyskinesia analysis, the LSM, pairwise difference, and 95% confidence intervals have been provided. In addition, 95% confidence intervals comparing each preladenant dose to rasagiline has been tabulated for each analysis. For the Responder analysis, proportion of Responders, odds ratio, and a 95% confidence interval for the odds ratio comparing rasagiline with placebo have been provided.

Multiplicity for the preladenant versus placebo comparisons in the Primary and Key Secondary Endpoints was controlled using a sequential testing procedure. Testing for the Primary and Key Secondary endpoints began with comparisons of the two highest doses of preladenant versus placebo (10 mg BID and 5 mg BID) in order of the 10 mg BID dose followed by the 5 mg BID dose; for each endpoint beginning with the Primary endpoint, then the proportion of Responders and last, the “on” time without troublesome dyskinesias endpoint. If each of these comparisons was statistically significant ($p \leq 0.049$) then testing continued with comparisons of the lowest dose, 2 mg BID, versus placebo for the same three endpoints. Testing continued until a non statistically significant difference was reached or all Primary and Key Secondary hypotheses were tested.

Safety Analysis: Treatment comparisons for pre-specified (Tier 1) events (including the incidence of elevated BP [systolic ≥180 mm Hg and/or diastolic ≥105 mm Hg], elevated LFTs [ALT and/or AST ≥3 x ULN with ≥ a 10% increase from Baseline], and suicidality incidence) were performed using the Miettinen and Nurminen method. The 95% confidence intervals for the pairwise differences between preladenant doses versus placebo, rasagiline versus placebo, and preladenant doses versus rasagiline have been provided. Between treatment group differences in the Epworth Sleepiness Scale score change from Baseline were evaluated using the same cLDA model as for the Primary Endpoint.

Commonly occurring adverse events were summarized by dose group using frequency counts, as well as incidence rates with 95% confidence intervals. Suicidal behavior and suicidal ideation were summarized by treatment group. Adverse events, vital signs, laboratory data, 12-lead electrocardiogram (ECG) parameters, and QUIP-RS score and Sleep Attack Questionnaire results have been listed and summarized by treatment group and time point; where applicable, values outside the normal range were flagged. Assessments of interest, liver function tests (LFTs) and BP, were summarized using descriptive statistics and graphs.

RESULTS:

Efficacy:

Preladenant 2 mg, 5 mg, and 10 mg BID did not demonstrate efficacy compared with placebo for the primary endpoint of change in “off” time from baseline to week 12 in patients with moderate to severe PD with motor fluctuations on stable doses of L dopa. Importantly, rasagiline the active control used in this study with demonstrated efficacy in this population also did not demonstrate statistical superiority over placebo on this endpoint. The changes from Baseline to Week 12 were similar among the treatment groups (0.8 hours to 1.1 hours decrease in average “off” time). There was no evidence of a dose response relationship among the three preladenant treatment groups.

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For the Key Secondary endpoint, the proportion of Responders (subjects obtaining at least a 30% reduction in mean "off" time from Baseline to Week 12), there were no differences between any of the treatment groups and placebo. Both the odds ratios and the proportions of Responders showed no statistically significant differences among preladenant-treated and placebo-treated groups. Differences between rasagiline and placebo were small and not clinically meaningful. The percent of subjects with at least a 30% decrease in "off" time at Week 12 was similar among the preladenant, placebo, and rasagiline treatment groups and ranged from 31.0% to 36.3%.

Similarly, for the second Key Secondary endpoint, there were no differences among the treatment arms for the endpoint of change in "on" time without troublesome dyskinesia from Baseline to Week 12. Baseline values were similar and ranged from 9.5 hours to 10.2 hours across the five treatment arms. "On" time without troublesome dyskinesia had larger increases in the preladenant treatment groups (0.8 hour, 0.9 hour and 0.5 hour for the 2, 5 and 10 mg bid doses respectively) and the rasagiline treatment group (0.7 hour) than the placebo group (0.4 hour); however, none of the preladenant vs placebo differences were statistically significant, nor was there a dose response.

None of the other efficacy endpoints demonstrated a consistent pattern suggestive of the potential efficacy of preladenant in moderate to severe PD subjects with motor fluctuations on stable doses of L dopa.

Post hoc analyses did not identify a single causal factor that could explain the finding of a failed study, but there were some notable findings:

- There was a difference in key efficacy parameters between subjects enrolled during the first vs the second half of the study, with a greater decrease in "off" time from baseline to week 12 in all active arms and a lower placebo effect found in subjects who enrolled in the first half.
- Treatment responses varied by region with the placebo responses highest in certain regions: Turkey, India, and Latin America. These regions also enrolled smaller numbers of subjects. In contrast, the treatment responses in the other regions, Eastern and Western Europe and North America were directionally as would be expected in that the preladenant and rasagiline arms had greater decreases in "off" time than placebo; however, these improvements were generally modest (less than 1 hour) and there was no evidence of a dose response within any of these regions.
- An analysis of the data removing high placebo responders did not alter the conclusions of this study as the treatment effect remained modest.

- **Safety:**

The percentage of subjects reporting at least 1 AE was similar among 2 mg 82 (53%), 5 mg 82 (54%), and 10 mg BID preladenant 86 (56%) groups and the rasagiline 84 (55%), and placebo 87 (56%) treatment groups. The discontinuation rates due to drug related AEs (5%, 9%, and 3%) for 2 mg BID, 5 mg BID, and 10 mg BID respectively were similar to placebo (8%). There were no marked differences in the rates of various types of AEs among the treatment groups. Overall, BID treatment with 2 mg, 5 mg, and 10 mg preladenant, placebo, and QD treatment with 1 mg rasagiline resulted in similar incidences of TEAE. Treatment related AEs occurring in more than 5% of subjects were constipation, dyskinesia, and headache.

Of the Tier 2 AEs, constipation was the only one with a significant difference estimate for the 10 mg BID preladenant treatment group compared with the placebo treatment group ($p \leq 0.001$).

Transient elevations in blood pressure showed no evidence of a dose response and no statistically significant differences between placebo and any of the preladenant treatment

groups were identified.

During the treatment phase, the incidence of SAEs in the preladenant and placebo treatment groups was similar while the rasagiline treatment group had a slightly higher incidence of SAEs. Overall, the incidences of SAEs were low and no greater than 1% in any of the treatment groups during the screening or treatment phase. There were no deaths in the preladenant or in the rasagiline treatment groups while one death occurred in the placebo treatment group. The subject died of respiratory arrest.

Evaluation of the overall hepatic related safety data (AEs and LFTs) revealed that 4 subjects had elevations in LFTs with ALT/AST values ≥ 3 x ULN + 10% increase post-baseline; one of which was associated with T BIL ≥ 2xULN that was associated with alcohol abuse. Of the incidences, one subject was on placebo treatment, and one subject on each of the preladenant doses, 2 mg, 5 mg, and 10 mg BID. All elevations returned to normal either on treatment or shortly after stopping study treatment. The elevation that was associated with T BIL≥ 2xULN occurred in the subject in the preladenant 10 mg BID group. This subject had a history of alcohol abuse, and an alcoholic binge event was reported by a family member as having occurred prior to the day of the lab draw. The event was addition additionally confounded by the potential use of allopurinol and aspirin. The elevation in total bilirubin had normalized by the next blood draw 7 days later and LFTs returned to normal suggesting that liver injury did not occur. Detailed summaries of the individual subject narratives and patient profile charts are provided in of Section 12.2.7.1.2.3.

The changes from Baseline over time for ALT, AST, T-BIL, and ALK-P were similar among the preladenant and the placebo treatment groups. The shift in values from baseline were similar across all treatment groups in ALT, AST, T BIL and ALK P with similar numbers of subjects having values that shifted from low to normal and from normal to high along with fewer who had values that shifted from high to normal. The mean changes in laboratory data from Baseline in AST, ALT, T-BIL, and ALK-P showed no dose related trend in the preladenant treatment groups, even though the highest elevations (5-8 X ULN) were found in the preladenant treatment groups. There were no clinically relevant changes in other laboratory values.

There were no clinically relevant changes in vital signs. Blood pressure was a closely monitored event and the change in SBP and DBP from pretreatment to post treatment on Day 1 demonstrated a modest elevation in BP which stabilized by the next clinic visit (2 weeks later) and on average was similar to baseline and placebo values.

Incidence of suicidal ideation based on the C-SSRS was similar between all treatment groups. The Incidence of potential intentional medication misuse was low and overall similar among the treatment groups.

The changes from baseline in total ESS at week 12 in the preladenant treated groups compared with placebo were similar with no statistically significant differences in the changes from baseline in mean total sleep time at week 12 between the preladenant and placebo treatment groups. The summary of the sleep attack questionnaire showed similar incidences of sleep attack between all treatment groups.

Counts of potential melanomas were higher in the rasagiline (3) and preladenant 10 mg BID (4) than in the placebo (1) or the preladenant 2 mg BID (1) and 5 mg BID (1) treatment groups.

CONCLUSIONS:

Safety:

- Preladenant was generally well tolerated in this trial.
- The percentages of subjects reporting at least 1 AE ranged from 53% to 57%, while TEAEs also ranging from 53% to 57%, were overall similar among the treatment groups. There were no marked differences in the rates of various types of AEs among the treatment groups. Of the Tier 2 AEs, constipation was the only one with a significant difference estimate which was between the 10 mg BID preladenant treatment group (10.5%) and the placebo treatment group (0.5%) with a P-value of $p \leq 0.001$. Discontinuation rates due to drug related AEs were small ($\leq$ 9%) and similar among the treatment groups.
- Incidences in other categories of AEs (ie any SAE, any serious drug-related AE and discontinuation due to an AE) were not significantly different between preladenant and placebo.
- Evaluation of the overall hepatic related safety data (AEs and LFTs) revealed that the incidence of elevation in LFTs to $\geq$ 3 x ULN and $\geq$ 10% increase from baseline was similar between preladenant and placebo. The degrees of elevations were higher in the individual preladenant groups. There was one case of LFT elevations associated with elevated Bilirubin which was confounded by a history of alcohol abuse and recent alcohol use and potentially the use of allopurinol and aspirin.
- Overall the changes from Baseline over time for the parameters ALT, AST, T-BIL, and ALK-P were similar among the preladenant and the placebo treatment groups. The amount of shift in ALT, AST, T BIL and ALK P and the mean changes in laboratory data from Baseline showed no dose related trends in the preladenant treatment groups. There were no clinically relevant changes in other laboratory values.
- Changes in SBP and DBP from pretreatment to post treatment on day 1 represented a small, transient increase which was attenuated by Week 2. Overall the changes in BP for the preladenant treatment groups were small and similar to the placebo treatment group.

Efficacy:

- This trial is considered failed and a definitive assessment of the efficacy of preladenant in moderate to severe PD cannot be made. None of the preladenant treatment arms or the active control, rasagiline, demonstrated statistical superiority over placebo for the primary endpoint of change from Baseline to Week 12 in “off” time. In addition, the magnitude of the change from baseline in “off” time from baseline to week 12 was much less than that observed in the phase 2b study and less than what has been historically observed for rasagiline.
- For the Key Secondary endpoint, the proportion of Responders (subjects obtaining at least a 30% reduction in mean “off” time from Baseline to Week 12), there was no separation between any of the treatment groups and placebo. Both the odds ratios and the proportions of Responders showed no statistically significant differences among preladenant or rasagiline-treated and placebo-treated groups.
- Similarly, for the second Key Secondary endpoint, there were no clinically meaningful differences for the endpoint of change in ON time without TD from Baseline to Week 12. All preladenant treatment groups and the rasagiline treatment group had larger increases in ON time without TD than the placebo group; however, none of the preladenant vs placebo differences were statistically significant, nor was there a dose response.

- None of the other efficacy endpoints demonstrated a consistent pattern suggestive of the potential efficacy of preladenant in moderate to severe PD subjects with motor fluctuations on stable doses of L dopa. This is confounded by the absence of efficacy that would have been expected from rasagiline.
- Post hoc analyses did not identify a single causal factor that could explain the finding of a failed study, but there were some notable findings:
  - There was a difference between the first and second half of the study with a greater decrease in "off" time from baseline to week 12 in all active arms and a lower placebo effect in the first half compared to subjects enrolled in the second half.
  - Treatment responses varied by region with the placebo responses highest in certain regions: Turkey, India, and Latin America. These regions also enrolled smaller numbers of subjects. In contrast, the treatment responses in the other regions, Eastern and Western Europe and North America were directionally as would be expected in that the preladenant and rasagiline arms had greater decreases in "off" time than placebo; however, these improvements were generally modest (less than 1 hour) and there was no evidence of a dose response within any of these regions.
  - An analysis of the data removing high placebo responders did not alter the conclusions of this study as the treatment effect remained modest.
  - There was no major impact of site size on the observed treatment group responses.