**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

| | | |
|---|---|---|
| **SPONSOR:** | Merck Sharp & Dohme Corp.,<br>a subsidiary of Merck & Co., Inc. | |
| **COMPOUND NAME:** | MK-3814/SCH 420814, Preladenant (PRL) in tablet form | |
| **INDICATION:** | Parkinson's Disease | |
| **PROTOCOL TITLE:** | A Phase 3, Double-Blind, Double-Dummy, Placebo- and Active-Controlled Dose-Range-Finding Efficacy and Safety Study of Preladenant in Subjects With Early Parkinson's Disease (Phase 3; Protocol No. P05664) | |
| **TRIAL IDENTIFIERS:** | Protocol Number: | 3814-024/P05664 |
| | Clinical Phase: | 3 |
| | EudraCT Number: | 2009-013552-72 |
| **ETHICS:** | This trial was conducted in conformance with applicable country or local requirements regarding ethical committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research.<br>[redacted] | |
| **TRIAL CENTERS:** | A total of 181 centers were approved to screen subjects. This trial was conducted at 153 trial centers: 28 in the United States; 8 in Argentina; 5 in Bulgaria; 6 in Canada; 6 in Chile; 4 in Colombia; 5 in Czech Republic; 1 in Finland; 4 in France; 9 in Germany; 5 in Hungary; 8 in India; 5 in Israel; 9 in Italy; 5 in Mexico; 6 in Peru; 8 in Poland; 7 in Russia; 9 in Spain; 3 in Sweden; 6 in Turkey; 5 in United Kingdom; and 1 in South Africa.<br>[redacted] | |

<table>
<tr><td>DESIGN:</td><td>This was a randomized, placebo- and active-controlled, double-blind trial designed to assess the efficacy and safety of preladenant 2, 5, and 10 mg twice daily in subjects with early PD who (at study start) were not yet receiving L-dopa or dopamine agonists.<br><br>The entire trial consisted of 2 parts. During Part 1 of the trial, subjects were randomized to one of five treatment groups (2 mg, 5 mg, or 10 mg of preladenant twice daily, placebo, or 1 mg rasagiline once daily) in a 1:1:1:1:1 ratio and treated for 26 weeks. Part 2 of the trial was an additional 26 weeks; subjects continued taking the same study treatment as in Part 1 except for the placebo subjects who were re-assigned to receive preladenant 5 mg twice daily. At the end of Part 1 the database was reviewed for quality and accuracy and locked and the treatment code unblinded for a planned analysis of the Part 1 data. A final analysis including the Part 2 data was conducted at the end of the study.<br><br>[redacted] Sample case report forms are not required for a non-submission aCSR. [redacted]<br><table><tr><td>Planned duration of main phase:</td><td>52 weeks</td></tr><tr><td>Planned duration of screening phase:</td><td>Up to 5 weeks</td></tr></table></td></tr>
<tr><td>Objectives</td><td>Primary Efficacy Objective: The Primary Efficacy Objective of this trial was to evaluate the efficacy of a range of preladenant doses compared with placebo in subjects with early Parkinson’s disease (PD) as measured by the sum of UPDRS Parts 2 and 3 scores (UPDRS2+3).<br><br>Primary Safety Objective: The Primary Safety Objective of this trial was to evaluate the safety and tolerability of preladenant compared with placebo in subjects with early PD.<br>Key Secondary Trial Objective: The Key Secondary Objective of this trial was to evaluate the efficacy of a range of preladenant doses compared with placebo in subjects with early PD as measured by the proportion of Responders and by the UPDRS Part 2 score.</td></tr>
</table>

| | | |
|---|---|---|
| Hypotheses | Hypothesis 1: At least the 10 mg twice daily dose of preladenant is superior to placebo as measured by the change from Baseline to Week 26 in the sum of UPDRS Parts 2 and 3 scores (UPDRS2+3).<br>Hypothesis 2: At least the 10 mg twice daily dose of preladenant is superior to placebo as measured by the proportion of subjects with at least a 20% improvement in UPDRS2+3 from Baseline at Week 26.<br>Hypothesis 3: At least the 10 mg twice daily dose of preladenant is superior to placebo as measured by the change from Baseline to Week 26 in the UPDRS Part 2 score. | |
| Treatment groups | PRL 2 mg BID | PRL, 52 weeks, 2 mg tablet, administered BID once in morning and again 8 hours later<br>204 subjects were randomized into Part 1 of which 166 entered Part 2 |
| | PRL 5 mg BID | PRL, 52 weeks, 5 mg tablet, administered BID once in morning and again 8 hours later<br>204 subjects were randomized into Part 1 of which 177 entered Part 2 |
| | PRL 10 mg BID | PRL, 52 weeks, 10 mg tablet, administered BID once in morning and again 8 hours later<br>206 subjects were randomized in Part 1 of which 167 entered Part 2 |
| | PLA/PRL 5 mg BID | Part 1:Placebo, 26 weeks, matching placebo tablet, administered BID once in morning and again 8 hours later,<br>Part 2: PRL, 26 weeks, 5 mg tablet, administered BID once in morning and again 8 hours later<br>204 subjects were randomized in Part 1 of which 177 entered Part 2 |
| | 1 mg Rasagiline QD | RAS, 52 weeks, 1 mg capsule, administered once daily in the morning<br>204 subjects in Part 1 of which 181 entered Part 2 |

## Clinical Supplies Table

| Clinical Material | Potency | Form/Packaging | Batch Numbers |
|---|---|---|---|
| Preladenant | 2 mg | Tablet | [redacted] |

| Clinical Material | Potency | Form/Packaging | Batch Numbers |
|---|---|---|---|
| Preladenant | 5 mg | Tablet | [redacted] |
| Preladenant | 10 mg | Tablet | |
| Placebo (Preladenant) | NA | Tablet | |
| Rasagiline | 1 mg | Capsule | |
| Placebo (Rasagiline) | NA | Capsule | |

| | | | |
|---|---|---|---|
| Endpoints and definitions | Primary efficacy endpoint | UPDRS 2+3 | The change from Baseline to Week 26 (End of Part 1 Treatment) in UPDRS2+3. |
| | Secondary efficacy endpoint | Responder<br><br>UPDRS 2 | • The proportion of Responders, where a Responder is defined as a subject with at least a 20% improvement in UPDRS2+3 from Baseline to Week 26 (End of Part 1 Treatment).<br>• The change from Baseline in the UPDRS Part 2 score (ADL) at Week 26. |
| | Prespecified safety endpoint | Tier 1 events | • SBP ≥180 mm Hg,<br>• DBP≥105 mm Hg,<br>• ALT≥3 x ULN with ≥10% increase from Baseline,<br>• AST≥3 x ULN with ≥10% increase from Baseline,<br>• C-SSRS Suicidality;<br>• Change from Baseline in Epworth Sleepiness Scale score. |

| | | | |
|---|---|---|---|
| Database lock | Part 1 Interim: 16-MAY-2013<br>End of trial: 23-AUG-2013 | Trial status | 07-OCT-2010 First subject first visit<br>16-JUL-2013 Last subject last visit<br>(Trial terminated early) |
| **RESULTS AND ANALYSIS:** | All analyses for efficacy and safety were performed according to the protocol [redacted]. Pharmacokinetic samples were analyzed for PRL according to the protocol [redacted] | | |

| **Analysis description** | **Primary Efficacy Analysis** |
|---|---|
| Analysis population and time point description | Analysis data sets are defined below:<br>Full Analysis Set (FAS): All randomized subjects with subjects excluded for the following reasons:<br>• Failure to receive at least one dose of study treatment.<br>• Lack of any post-Randomization endpoint data subsequent to at least one dose of study treatment.<br>• Lack of Baseline data for those analyses that require Baseline data.<br><br>Efficacy data collected after the start of PD Treatment(s) in Addition to Baseline PD Treatment(s) were excluded from the FAS in Part 1. In the Part 2 exploratory analyses, this data was excluded from the main analysis, but is included in a sensitivity analysis. |
| Summary | Based on results from Part 1 data, this study with placebo and active control is a failed study. All of the preladenant treatment arms and the active-control arm, rasagiline 1mg QD, failed to demonstrate statistical difference versus placebo. Of note, preladenant 2mg BID was statistically significantly worse than placebo in the primary and one of the key secondary efficacy endpoints ($p<0.01$).<br><br>There was no additional efficacy analyses performed in Part 2 of the early terminated study. |
| **Analysis description** | **Key Secondary Efficacy Analysis** |
| Analysis population and time point description | FAS |
| Summary | None of the PRL treatment group demonstrated a statistically significant and clinically meaningful difference vs. placebo at week 26 in the key secondary endpoints. |

| **Analysis description** | **Safety Analysis** |
|---|---|
| Analysis population and time point description | All Subjects as Treated Set (ASaT): All subjects who received at least one dose of study treatment. |
| Summary | The overall rates by type of event were similar among the treatment arms and not different than placebo. |

## Subject Disposition

One thousand and twenty-two subjects were randomized and of those 1007 were treated with study medication. Six hundred and six subjects were treated with PRL, 198 with placebo and 203 with Rasagiline in Part 1. Five hundred and ten subjects (84%) of the PRL treated subjects completed Part 1 and continued with the same PRL treatment in Part 2. One hundred seventy seven subjects (89%) of the placebo treated subjects completed Part 1 and entered Part 2 with PRL 5 mg BID treatment. One hundred eighty one subjects (89%) of the rasagiline treated subjects completed Part 1 and continued with the same rasagiline treatment in Part 2. Eight hundred and sixty-eight subjects were treated in Part 2 from which 585 (67%) completed the study and 212 (24.4%) were terminated early due to study closure. [redacted]

## Subject Disposition-Treatment Phase (All Subjects Randomized)—Part 1

| Subject Disposition | Preladenant 2mg BID | | Preladenant 5mg BID | | Preladenant 10mg BID | | All Preladenant | | Placebo | | Rasagiline 1mg QD | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Randomized | 204 | (100) | 204 | (100) | 206 | (100) | 614 | (100) | 204 | (100) | 204 | (100) |
| Treated | 200 | (98) | 202 | (99) | 204 | (99) | 606 | (99) | 198 | (97) | 203 | (100) |
| Discontinued Part 1 Treatment | 34 | (17) | 25 | (12) | 37 | (18) | 96 | (16) | 21 | (10) | 22 | (11) |
| Adverse Event | 13 | (6) | 8 | (4) | 18 | (9) | 39 | (6) | 7 | (3) | 6 | (3) |
| Treatment Failure | 3 | (1) | 0 | | 3 | (1) | 6 | (1) | 1 | (<1) | 2 | (1) |
| Lost To Follow-Up | 0 | | 0 | | 1 | (<1) | 1 | (<1) | 1 | (<1) | 0 | |
| Subject Withdrew Consent | 11 | (5) | 13 | (6) | 8 | (4) | 32 | (5) | 8 | (4) | 9 | (4) |
| Non-Compliance With Protocol | 2 | (1) | 1 | (<1) | 3 | (1) | 6 | (1) | 3 | (1) | 2 | (1) |
| Did Not Meet Protocol Eligibility | 3 | (1) | 1 | (<1) | 2 | (1) | 6 | (1) | 1 | (<1) | 3 | (1) |
| Administrative | 2 | (1) | 2 | (1) | 2 | (1) | 6 | (1) | 0 | | 0 | |
| Completed Part1 Treatment | 166 | (81) | 177 | (87) | 167 | (81) | 510 | (83) | 177 | (87) | 181 | (89) |
| Entered Part 2 Treatment | 166 | (81) | 177 | (87) | 167 | (81) | 510 | (83) | 177 | (87) | 181 | (89) |

[redacted]

## Subject Disposition-Treatment Phase (All Subjects Randomized)—Part 2

| Subject Disposition | Preladenant 2mg BID | | Preladenant 5mg BID | | Preladenant 10mg BID | | All Preladenant | | PLA/PRL 5mg BID | | Rasagiline 1mg QD | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Entered Part 2 | 166 | (100) | 177 | (100) | 167 | (100) | 510 | (100) | 177 | (100) | 181 | (100) |
| Discontinued Treatment Phase | 59 | (36) | 61 | (34) | 58 | (35) | 178 | (35) | 50 | (28) | 55 | (30) |
| Adverse Event | 7 | (4) | 6 | (3) | 8 | (5) | 21 | (4) | 3 | (2) | 4 | (2) |
| Treatment Failure | 0 | | 1 | (1) | 2 | (1) | 3 | (1) | 0 | | 1 | (1) |
| Lost To Follow-Up | 1 | (1) | 0 | | 0 | | 1 | (<1) | 0 | | 1 | (1) |
| Subject Withdrew Consent | 8 | (5) | 4 | (2) | 12 | (7) | 24 | (5) | 7 | (4) | 3 | (2) |
| Non-Compliance With Protocol | 0 | | 1 | (1) | 0 | | 1 | (<1) | 2 | (1) | 0 | |
| Administrative | 43 | (26) | 49 | (28) | 36 | (22) | 128 | (25) | 38 | (21) | 46 | (25) |
| Completed Part 2 Treatment | 107 | (64) | 116 | (66) | 109 | (65) | 332 | (65) | 127 | (72) | 126 | (70) |

[redacted]

Overall, baseline demographics and disease characteristics were similar among the treatment groups. More male subjects (58%) and white subjects (84%) were randomized in the trial. The mean ages of subjects were 63.0, 62.3, 63.8, 63.3, and 62.9 for the PRL 2 mg BID, 5 mg BID, 10 mg BID, PLA/PRL 5 mg BID and rasagiline 1 mg QD treatment groups respectively, with an overall age range of 30 to 86 years. The mean BMI was 27.04, 26.66, 26.72, 26.93 and 26.87 for the PRL 2 mg BID, 5 mg BID, 10 mg BID, PLA/PRL 5 mg BID and rasagiline 1 mg QD treatment groups respectively,with an overall range of 16.2 to 47.8. Baseline disease severity as measured by the Hoehn & Yahr scale was similar among all PRL and Placebo/PRL 5 mg BID groups with slight differences for subjects randomized to Rasagaline 1 mg QD. There were fewer subjects classified as H&Y stage 2 (34% in Rasagiline 1 mg QD vs 46% and 48% in all PRL and Placebo/PRL 5 mg BID, respectively) and more with stage 3 (12% in Rasagiline 1 mg QD vs 7% and 3% in all PRL and Placebo/PRL 5 mg BID and, respectively). The mean and median years of PD history were 1.0 and 0.4 years for all PRL, 1.02 and 0.4 years for PLA/PRL 5 mg BID and 0.9 and 0.3 years for Rasagiline 1 mg QD treatment groups respectively, with an overall range of 0 to 5 years. Incidences of prior history of L-Dopa usage was 8%, 3% and 7% for all PRL, PLA/PRL 5 mg BID and and Rasagiline 1 mg QD treatment groups respectively.

## Summary of Demographics and Baseline Characteristics All subjects as Randomized

| | Preladenant 2mg BID n=204 | Preladenant 5mg BID n=204 | Preladenant 10mg BID n=206 | All Preladenant n=614 | PLA/PRL 5mg BID n=204 | Rasagiline 1mg QD n=204 |
|---|---|---|---|---|---|---|
| Sex (n,%) | | | | | | |
| Female | 78 ( 38 ) | 90 ( 44 ) | 90 ( 44 ) | 258 ( 42 ) | 82 ( 40 ) | 85 ( 42 ) |
| Male | 126 ( 62 ) | 114 ( 56 ) | 116 ( 56 ) | 356 ( 58 ) | 122 ( 60 ) | 119 ( 58 ) |
| Race (n,%) | | | | | | |
| White | 173 ( 85 ) | 171 ( 84 ) | 174 ( 84 ) | 518 ( 84 ) | 169 ( 83 ) | 170 ( 83 ) |
| Non-White | 31 ( 15 ) | 33 ( 16 ) | 32 ( 16 ) | 96 ( 16 ) | 35 ( 17 ) | 34 ( 17 ) |
| American Indian or* Alaskan Native | 0 | 0 | 0 | 0 | 0 | 1 ( <1 ) |
| Asian | 10 ( 5 ) | 14 ( 7 ) | 10 ( 5 ) | 34 ( 6 ) | 12 ( 6 ) | 11 ( 5 ) |
| Black or African American | 1 ( <1 ) | 1 ( <1 ) | 1 ( <1 ) | 3 ( <1 ) | 1 ( <1 ) | 2 ( 1 ) |
| Multiracial | 20 ( 10 ) | 18 ( 9 ) | 21 ( 10 ) | 59 ( 10 ) | 22 ( 11 ) | 20 ( 10 ) |
| Ethnicity (n,%) | | | | | | |
| Hispanic or Latino | 60 ( 29 ) | 51 ( 25 ) | 62 ( 30 ) | 173 ( 28 ) | 56 ( 27 ) | 56 ( 27 ) |
| Not Hispanic or Latino | 144 ( 71 ) | 153 ( 75 ) | 144 ( 70 ) | 441 ( 72 ) | 148 ( 73 ) | 148 ( 73 ) |

| | Preladenant 2mg BID n=204 | Preladenant 5mg BID n=204 | Preladenant 10mg BID n=206 | All Preladenant n=614 | PLA/PRL 5mg BID n=204 | Rasagiline 1mg QD n=204 |
|---|---|---|---|---|---|---|
| Age (yrs) | | | | | | |
| Mean (SD) | 63.0 (10.5) | 62.3 (10.2) | 63.8 (11.1) | 63.0 (10.6) | 63.3 (10.0) | 62.9 (10.2) |
| Median | 64.5 | 63.0 | 65.0 | 64.0 | 64.0 | 63.0 |
| Range | 30 - 83 | 33 - 85 | 30 - 84 | 30 - 85 | 31 - 84 | 35 - 86 |
| Age (n,%) | | | | | | |
| 30 - <55 | 42 ( 21 ) | 40 ( 20 ) | 40 ( 19 ) | 122 ( 20 ) | 36 ( 18 ) | 38 ( 19 ) |
| 55 - <65 | 60 ( 29 ) | 76 ( 37 ) | 61 ( 30 ) | 197 ( 32 ) | 70 ( 34 ) | 74 ( 36 ) |
| 65 - <75 | 77 ( 38 ) | 64 ( 31 ) | 69 ( 33 ) | 210 ( 34 ) | 70 ( 34 ) | 64 ( 31 ) |
| >=75 | 25 ( 12 ) | 24 ( 12 ) | 36 ( 17 ) | 85 ( 14 ) | 28 ( 14 ) | 28 ( 14 ) |
| Weight (kg) | | | | | | |
| Mean (SD) | 76.26 (14.74) | 74.74 (15.23) | 74.29 (14.81) | 75.09 (14.93) | 75.34 (14.81) | 75.68 (14.69) |
| Median | 75.00 | 74.00 | 74.00 | 74.00 | 74.30 | 75.40 |
| Range | 46.6 - 127.5 | 40.0 - 132.0 | 39.0 - 120.3 | 39.0 - 132.0 | 45.4 - 130.0 | 44.5 - 132.0 |
| Missing | 7 | 3 | 5 | 15 | 7 | 3 |

| | Preladenant 2mg BID n=204 | Preladenant 5mg BID n=204 | Preladenant 10mg BID n=206 | All Preladenant n=614 | PLA/PRL 5mg BID n=204 | Rasagiline 1mg QD n=204 |
|---|---|---|---|---|---|---|
| Height (cm) | | | | | | |
| Mean (SD) | 167.81 (10.53) | 167.29 (10.05) | 166.28 ( 9.88) | 167.12 (10.16) | 167.00 ( 9.70) | 167.91 ( 9.36) |
| Median | 168.00 | 167.50 | 165.05 | 167.00 | 166.00 | 168.00 |
| Range | 134.0 - 195.6 | 144.0 - 192.0 | 140.0 - 192.0 | 134.0 - 195.6 | 145.0 - 193.0 | 143.0 - 189.0 |
| Missing | 6 | 4 | 4 | 14 | 7 | 5 |
| BMI | | | | | | |
| Mean (SD) | 27.04 ( 4.18) | 26.66 ( 4.54) | 26.72 ( 3.95) | 26.81 ( 4.23) | 26.93 ( 4.27) | 26.87 ( 4.66) |
| Median | 26.70 | 26.20 | 26.30 | 26.40 | 26.10 | 26.20 |
| Range | 18.9 - 42.0 | 17.6 - 43.9 | 16.2 - 44.8 | 16.2 - 44.8 | 18.7 - 43.2 | 17.7 - 47.8 |
| Missing | 7 | 4 | 5 | 16 | 7 | 5 |
| Hoehn and Yahr Staging (n,%) | | | | | | |
| Stage 1 | 36 ( 18 ) | 42 ( 21 ) | 37 ( 18 ) | 115 ( 19 ) | 45 ( 22 ) | 49 ( 24 ) |
| Stage 1.5 | 31 ( 15 ) | 31 ( 15 ) | 40 ( 19 ) | 102 ( 17 ) | 31 ( 15 ) | 30 ( 15 ) |
| Stage 2 | 90 ( 44 ) | 106 ( 52 ) | 89 ( 43 ) | 285 ( 46 ) | 97 ( 48 ) | 70 ( 34 ) |

| | Preladenant 2mg BID n=204 | Preladenant 5mg BID n=204 | Preladenant 10mg BID n=206 | All Preladenant n=614 | PLA/PRL 5mg BID n=204 | Rasagiline 1mg QD n=204 |
|---|---|---|---|---|---|---|
| Stage 2.5 | 27 ( 13 ) | 16 ( 8 ) | 29 ( 14 ) | 72 ( 12 ) | 25 ( 12 ) | 31 ( 15 ) |
| Stage 3 | 20 ( 10 ) | 9 ( 4 ) | 11 ( 5 ) | 40 ( 7 ) | 6 ( 3 ) | 24 ( 12 ) |
| Baseline MoCA | | | | | | |
| Mean (SD) | 27.99 ( 1.73) | 28.02 ( 1.57) | 27.95 ( 1.85) | 27.99 ( 1.72) | 28.06 ( 1.59) | 28.09 ( 1.65) |
| Median | 28.00 | 28.00 | 28.00 | 28.00 | 28.00 | 28.00 |
| Range | 23.0 - 30.0 | 23.0 - 30.0 | 22.0 - 30.0 | 22.0 - 30.0 | 22.0 - 30.0 | 23.0 - 30.0 |
| Smoking Daily Use (n,%) | | | | | | |
| None | 185 ( 91 ) | 193 ( 95 ) | 195 ( 95 ) | 573 ( 93 ) | 189 ( 93 ) | 187 ( 92 ) |
| <1 pack per day | 16 ( 8 ) | 9 ( 4 ) | 8 ( 4 ) | 33 ( 5 ) | 9 ( 4 ) | 8 ( 4 ) |
| 1-2 packs per day | 0 | 0 | 1 ( <1 ) | 1 ( <1 ) | 2 ( 1 ) | 1 ( <1 ) |
| Missing | 3 ( 1 ) | 2 ( 1 ) | 2 ( 1 ) | 7 ( 1 ) | 4 ( 2 ) | 8 ( 4 ) |
| Caffeine Daily Use (n,%) | | | | | | |
| None | 59 ( 29 ) | 59 ( 29 ) | 70 ( 34 ) | 188 ( 31 ) | 77 ( 38 ) | 56 ( 27 ) |
| >None - 1 cup/glass per day | 68 ( 33 ) | 69 ( 34 ) | 77 ( 37 ) | 214 ( 35 ) | 57 ( 28 ) | 70 ( 34 ) |

| | Preladenant 2mg BID n=204 | Preladenant 5mg BID n=204 | Preladenant 10mg BID n=206 | All Preladenant n=614 | PLA/PRL 5mg BID n=204 | Rasagiline 1mg QD n=204 |
|---|---|---|---|---|---|---|
| >1 cups/glasses per day | 74 ( 36 ) | 74 ( 36 ) | 57 ( 28 ) | 205 ( 33 ) | 66 ( 32 ) | 70 ( 34 ) |
| Missing | 3 ( 1 ) | 2 ( 1 ) | 2 ( 1 ) | 7 ( 1 ) | 4 ( 2 ) | 8 ( 4 ) |
| Alcohol Daily Use (n,%) | | | | | | |
| None | 127 ( 62 ) | 133 ( 65 ) | 134 ( 65 ) | 394 ( 64 ) | 138 ( 68 ) | 127 ( 62 ) |
| <1 drink per day | 68 ( 33 ) | 54 ( 26 ) | 60 ( 29 ) | 182 ( 30 ) | 54 ( 26 ) | 59 ( 29 ) |
| 1-2 drinks per day | 6 ( 3 ) | 15 ( 7 ) | 10 ( 5 ) | 31 ( 5 ) | 8 ( 4 ) | 10 ( 5 ) |
| Missing | 3 ( 1 ) | 2 ( 1 ) | 2 ( 1 ) | 7 ( 1 ) | 4 ( 2 ) | 8 ( 4 ) |
| Family History of CHD | | | | | | |
| No | 140 ( 69 ) | 140 ( 69 ) | 127 ( 62 ) | 407 ( 66 ) | 132 ( 65 ) | 130 ( 64 ) |
| Unknown | 18 ( 9 ) | 15 ( 7 ) | 21 ( 10 ) | 54 ( 9 ) | 25 ( 12 ) | 17 ( 8 ) |
| Yes | 7 ( 3 ) | 12 ( 6 ) | 8 ( 4 ) | 27 ( 4 ) | 3 ( 1 ) | 7 ( 3 ) |
| Missing | 39 ( 19 ) | 37 ( 18 ) | 50 ( 24 ) | 126 ( 21 ) | 44 ( 22 ) | 50 ( 25 ) |
| PD History (Yrs) | | | | | | |
| Mean (SD) | 0.98 ( 1.20) | 1.05 ( 1.20) | 0.98 ( 1.13) | 1.00 ( 1.17) | 1.02 ( 1.23) | 0.90 ( 1.20) |

| | Preladenant 2mg BID n=204 | Preladenant 5mg BID n=204 | Preladenant 10mg BID n=206 | All Preladenant n=614 | PLA/PRL 5mg BID n=204 | Rasagiline 1mg QD n=204 |
|---|---|---|---|---|---|---|
| Median | 0.40 | 0.50 | 0.40 | 0.40 | 0.40 | 0.30 |
| Range | 0.0 - 5.0 | 0.0 - 5.0 | 0.0 - 4.6 | 0.0 - 5.0 | 0.0 - 4.7 | 0.0 - 4.9 |
| Missing | 1 | 0 | 2 | 3 | 3 | 3 |
| Prior History of L-Dopa Use | | | | | | |
| No | 185 ( 91 ) | 189 ( 93 ) | 190 ( 92 ) | 564 ( 92 ) | 198 ( 97 ) | 190 ( 93 ) |
| Yes | 19 ( 9 ) | 15 ( 7 ) | 16 ( 8 ) | 50 ( 8 ) | 6 ( 3 ) | 14 ( 7 ) |

[redacted]

## Efficacy

The summary of Part 1 results in primary and key secondary endpoints are shown in the following table and figure. Within the preladenant arms, the smallest response was observed in the 2mg BID dose arm and the largest response was observed in the 10mg BID dose arm; however, the placebo arm had the highest response of all. Subjects on rasagiline reported responses similar to the preladenant 10mg BID arm. All of the preladenant treatment arms and the active-control arm, rasagiline 1 mg QD, failed to demonstrate a statistically significant better efficacy vs. placebo. Part 1 results indicated this study with placebo and active control is a failed study. Due to the failed placebo and active control Part 1 of the study, no additional efficacy analyses were performed in Part 2 of the terminated study.

Summary of Primary and Key Secondary Efficacy Results at Week 26

| Efficacy Parameter | | Estimated Response | | | | |
|---|---|---|---|---|---|---|
| | | PRL 2 mg BID N[c]=195 | PRL 5 mg BID N[c]=202 | PRL 10 mg BID N[c]=200 | Placebo N[c]=195 | RAS 1 mg QD N[c]=195 |
| UPDRS Score, Part II and III Combined | CFB | 0.30 | -1.00 | -1.80 | -2.20 | -1.90 |
| | Diff vs PBO (95% CI) [d] | 2.60 (0.86, 4.30) | 1.30 (-0.41, 2.94) | 0.40 (-1.29, 2.11) | | 0.30 (-1.35, 2.03) |
| | p-value [d] | 0.0033 | 0.1382 | 0.6378 | | 0.6923 |
| Percent Responders | CFB | 25.9% | 29.5% | 31.5% | 35.2% | 33.1% |
| | Diff vs PBO (95% CI)[a] | -9.7% (-21.0, 1.82) | -6.3% (-17.6, 5.05) | -3.7% (-15.2, 7.99) | | -2.3% (-13.9, 9.24) |
| | p-value[b] | 0.0785 | 0.2735 | 0.4823 | | 0.6827 |
| UPDRS Score, Part II | CFB | 0.30 | 0.10 | -0.20 | -0.40 | -0.20 |
| | Diff vs PBO (95% CI) [d] | 0.70 (0.09, 1.27) | 0.50 (-0.11, 1.04) | 0.20 (-0.42, 0.75) | | 0.10 (-0.45, 0.70) |
| | p-value [d] | 0.0235 | 0.1093 | 0.5756 | | 0.6657 |

Source: Tables B1.1.1, B1.2.1, B1.3

CFB= Change from Baseline

a: Based on Miettinen and Nurminen method using model-based adjusted effective sample size

b: p-value is for the estimated Odds Ratio based on a generalized linear mixed model with baseline UPDRS2+3 as a covariate and treatment-by-time interaction as fixed effect and patient as random effect.

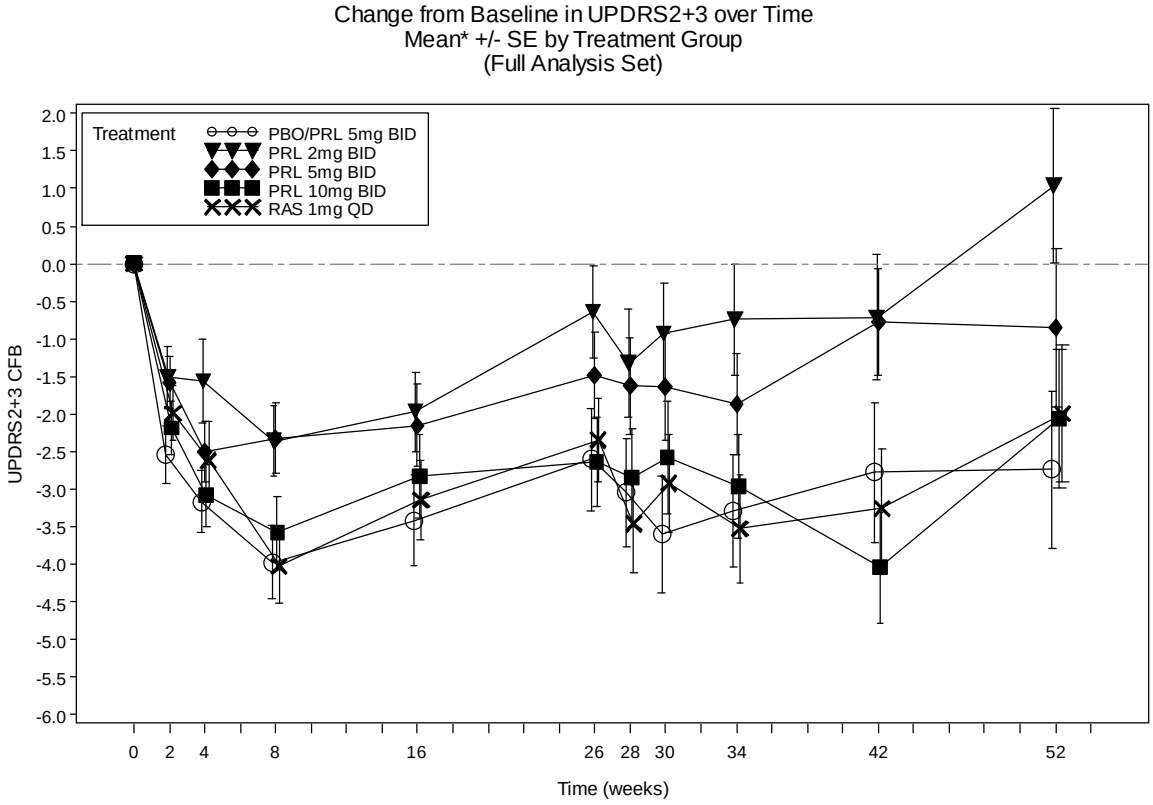
c: N represents the number of randomized and treated subjects with at least one post-baseline value.

d: These rows differ slightly from those issued at the time of the Early results memo. The difference was identified at the time of CSR writing but it did not significantly alter the results of the study.

[redacted]

[redacted]

The figure below shows the primary endpoint, change from baseline in UPDRS2+3, by treatment group and week over the entire study period. Results from later time points should be viewed with caution as 33% of the subjects did not complete Part 2 of the study. At the end of study Part 1 (Week 26), the response at 2, 5, 10 mg BID PRL doses ranged from 0.3, -1.0, -1.8. The rasagiline 1 mg QD response of -1.9 was similar to that of PRL 10 mg BID. However, placebo had the strongest response at Week 26 of -2.2 leading to the failed study.




## Safety

The clinical adverse experience summary table presents an overview of the number and percentage of subjects with AEs, according to types of AEs. In Part 1, the AE percentages were slightly higher in the preladenant treated subjects than the placebo and rasagiline 1 mg QD treatment groups. Fifty six percent of subjects treated with preladenant vs. 52 % for both placebo and rasagiline 1 mg QD treated subjects experienced at least 1 adverse event. Discontinuations due to an adverse event were 7% in preladenant treatment group compared to 4% and 3% for placebo and rasagiline 1 mg QD treatment groups, respectively. There were 10 subjects discontinued from the trial because of an SAE, 3 subjects in the preladenant 5 mg BID group, 4 subjects in the preladenant 10 mg BID group, 1 subject in the placebo group, and 2 subjects in the rasagiline 1 mg QD treatment group.

P05664
Part 1 Only - All Treated Subjects
Clinical Adverse Experience
Summary
Number of Subjects (%)

| Number (%) of subjects with: | Preladenant 2mg BID n=200 | Preladenant 5mg BID n=202 | Preladenant 10mg BID n=204 | All Preladenant n=606 | Placebo n=198 | Rasagiline 1mg QD n=203 |
|---|---|---|---|---|---|---|
| One or more adverse events | 108 (54) | 110 (54) | 121 (59) | 339 (56) | 102 (52) | 105 (52) |
| Drug-related adverse events | 50 (25) | 47 (23) | 64 (31) | 161 (27) | 42 (21) | 59 (29) |
| Serious adverse events | 4 (2) | 5 (2) | 8 (4) | 17 (3) | 3 (2) | 9 (4) |
| Serious drug-related adverse events | 0 | 3 (1) | 2 (1) | 5 (1) | 1 (1) | 2 (1) |
| Death | 0 | 0 | 1 (<1) | 1 (<1) | 0 | 0 |
| Discontinuation due to adverse event | 13 (7) | 8 (4) | 20 (10) | 41 (7) | 8 (4) | 6 (3) |
| Discontinuation due to drug-related adverse event | 6 (3) | 7 (3) | 13 (6) | 26 (4) | 6 (3) | 6 (3) |
| Discontinuation due to serious adverse event | 0 | 3 (1) | 4 (2) | 7 (1) | 1 (1) | 2 (1) |
| Discontinuation due to serious drug-related adverse event | 0 | 3 (1) | 1 (<1) | 4 (1) | 0 | 2 (1) |

[redacted]

Similarly, the AE percentages were slightly higher in the preladenant and placebo/ preladenant treated subjects than rasagiline 1 mg QD treatment group in Part 2. Sixty eight percent of subjects treated with preladenant or placebo/ preladenant vs. 66 % for rasagiline 1 mg QD treated subjects experienced at least 1 adverse event in Part 2. Discontinuations due to an adverse event were 4% in preladenant treatment group compared to 2% and 2% for placebo/ preladenant 5 mg BID and rasagiline 1 mg QD treatment groups, respectively. There were 5 subjects discontinued from the trial because of an SAE, 2 subjects in the preladenant 2 mg BID group, 2 subjects in the preladenant 10 mg BID group, and 1 subject in the rasagiline treatment group.

P05664
Part 2 Only - All Treated Subjects
Clinical Adverse Experience
Summary
Number of Subjects (%)

| Number (%) of subjects with: | Preladenant 2mg BID n=166 | Preladenant 5mg BID n=177 | Preladenant 10mg BID n=167 | All Preladenant n=510 | Placebo / Preladenant 5mg BID n=177 | Rasagiline 1mg QD n=181 |
|---|---|---|---|---|---|---|
| One or more adverse events | 116 (70) | 120 (68) | 113 (68) | 349 (68) | 120 (68) | 119 (66) |
| Drug-related adverse events | 57 (34) | 48 (27) | 61 (37) | 166 (33) | 56 (32) | 69 (38) |
| Serious adverse events | 9 (5) | 2 (1) | 11 (7) | 22 (4) | 5 (3) | 13 (7) |
| Serious drug-related adverse events | 1 (1) | 0 | 1 (1) | 2 (<1) | 0 | 1 (1) |
| Death | 0 | 0 | 1 (1) | 1 (<1) | 0 | 0 |
| Discontinuation due to adverse event | 7 (4) | 5 (3) | 8 (5) | 20 (4) | 3 (2) | 4 (2) |
| Discontinuation due to drug-related adverse event | 3 (2) | 3 (2) | 4 (2) | 10 (2) | 2 (1) | 3 (2) |
| Discontinuation due to serious adverse event | 2 (1) | 0 | 2 (1) | 4 (1) | 0 | 1 (1) |
| Discontinuation due to serious drug-related adverse event | 0 | 0 | 0 | 0 | 0 | 0 |

[redacted]

The overall amount of discontinuations due to serious drug related AEs was ≤1 % for all treatment groups within the study. There was one death during Part 1 (hemorrhagic cerebrovascular stroke in the preladenant 10 mg BID-treated subject) and one during Part 2 (sudden cardiac death in the preladenant 10 mg BID-treated subject).

[redacted]. Reasons for discontinuation after administration of trial medication are shown in the subject disposition table; [redacted]

The most common adverse events for both Part 1 and Part 2 are presented below.

## Part 1 Only All Treated Subjects

## Summary of Treatment Emergent Adverse Events (5% Incidence)

| | Preladenant 2mg BID | Preladenant 5mg BID | Preladenant 10mg BID | All Preladenant | Placebo | Rasagiline 1mg QD |
|---|---|---|---|---|---|---|
| | n=200 | n=202 | n=204 | n=606 | n=198 | n=203 |
| SUBJECTS REPORTING ANY ADVERSE EVENT | 105 (53) | 107 (53) | 120 (59) | 332 (55) | 98 (49) | 101 (50) |
| GASTROINTESTINAL DISORDERS | | | | | | |
| CONSTIPATION | 5 (3) | 9 (4) | 11 (5) | 25 (4) | 5 (3) | 3 (1) |
| INJURY, POISONING AND PROCEDURAL COMPLICATIONS | | | | | | |
| FALL | 3 (2) | 10 (5) | 5 (2) | 18 (3) | 4 (2) | 3 (1) |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS | | | | | | |
| BACK PAIN | 5 (3) | 10 (5) | 8 (4) | 23 (4) | 6 (3) | 5 (2) |
| NERVOUS SYSTEM DISORDERS | | | | | | |
| DIZZINESS | 6 (3) | 11 (5) | 5 (2) | 22 (4) | 9 (5) | 10 (5) |
| HEADACHE | 11 (6) | 9 (4) | 15 (7) | 35 (6) | 5 (3) | 8 (4) |
| TREMOR | 8 (4) | 7 (3) | 3 (1) | 18 (3) | 10 (5) | 6 (3) |
| VASCULAR DISORDERS | | | | | | |
| HYPERTENSION | 3 (2) | 8 (4) | 10 (5) | 21 (3) | 9 (5) | 9 (4) |

[redacted]

## Part 2 only All Treated Subjects

## Summary of Treatment Emergent Adverse Events (5% Incidence)

| | Preladenant 2mg BID | Preladenant 5mg BID | Preladenant 10mg BID | All Preladenant | PLA/PRL 5mg BID | Rasagiline 1mg QD |
|---|---|---|---|---|---|---|
| | n=166 | n=177 | n=167 | n=510 | n=177 | n=181 |
| SUBJECTS REPORTING ANY ADVERSE EVENT | 116 (70) | 120 (68) | 113 (68) | 349 (68) | 120 (68) | 119 (66) |
| GASTROINTESTINAL DISORDERS | | | | | | |
| CONSTIPATION | 6 (4) | 8 (5) | 12 (7) | 26 (5) | 12 (7) | 7 (4) |
| NAUSEA | 4 (2) | 5 (3) | 10 (6) | 19 (4) | 9 (5) | 7 (4) |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | | | | | | |
| FATIGUE | 6 (4) | 6 (3) | 7 (4) | 19 (4) | 6 (3) | 11 (6) |
| INFECTIONS AND INFESTATIONS | | | | | | |
| NASOPHARYNGITIS | 13 (8) | 8 (5) | 11 (7) | 32 (6) | 11 (6) | 9 (5) |
| UPPER RESPIRATORY TRACT INFECTION | 3 (2) | 6 (3) | 8 (5) | 17 (3) | 2 (1) | 6 (3) |
| URINARY TRACT INFECTION | 2 (1) | 7 (4) | 6 (4) | 15 (3) | 6 (3) | 9 (5) |
| INJURY, POISONING AND PROCEDURAL COMPLICATIONS | | | | | | |
| FALL | 5 (3) | 14 (8) | 8 (5) | 27 (5) | 9 (5) | 8 (4) |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS | | | | | | |
| BACK PAIN | 5 (3) | 16 (9) | 9 (5) | 30 (6) | 12 (7) | 12 (7) |
| PAIN IN EXTREMITY | 4 (2) | 9 (5) | 6 (4) | 19 (4) | 4 (2) | 4 (2) |
| NERVOUS SYSTEM DISORDERS | | | | | | |
| DIZZINESS | 8 (5) | 10 (6) | 7 (4) | 25 (5) | 11 (6) | 16 (9) |
| HEADACHE | 17 (10) | 11 (6) | 16 (10) | 44 (9) | 11 (6) | 12 (7) |
| SOMNOLENCE | 7 (4) | 9 (5) | 5 (3) | 21 (4) | 8 (5) | 9 (5) |

| | Preladenant 2mg BID | Preladenant 5mg BID | Preladenant 10mg BID | All Preladenant | PLA/PRL 5mg BID | Rasagiline 1mg QD |
|---|---|---|---|---|---|---|
| | n=166 | n=177 | n=167 | n=510 | n=177 | n=181 |
| TREMOR | 14 (8) | 17 (10) | 8 (5) | 39 (8) | 16 (9) | 11 (6) |
| PSYCHIATRIC DISORDERS | | | | | | |
| DEPRESSION | 10 (6) | 9 (5) | 7 (4) | 26 (5) | 5 (3) | 2 (1) |
| INSOMNIA | 10 (6) | 8 (5) | 7 (4) | 25 (5) | 7 (4) | 12 (7) |
| VASCULAR DISORDERS | | | | | | |
| HYPERTENSION | 3 (2) | 9 (5) | 12 (7) | 24 (5) | 12 (7) | 10 (6) |

[redacted]

ALT elevations in Part 1 and Part 2 are summarized in the table below. In summary:

- there were no Hy's Law cases;
- In both Part 1 and 2 of the study preladenant 10mg BID had the highest rate of ALT increases above 1.5xULN;
- In Part 1 of the study ALT increases > 3xULN were primarily in the preladenant arms; but in Part 2, rates were more similar in the PRL and RAS arms
- AST results were similar overall, but had a fewer cases of increased values >3xULN than ALT.

P05664
Incidence (N) of Categorical Change in ALT – Highest Result

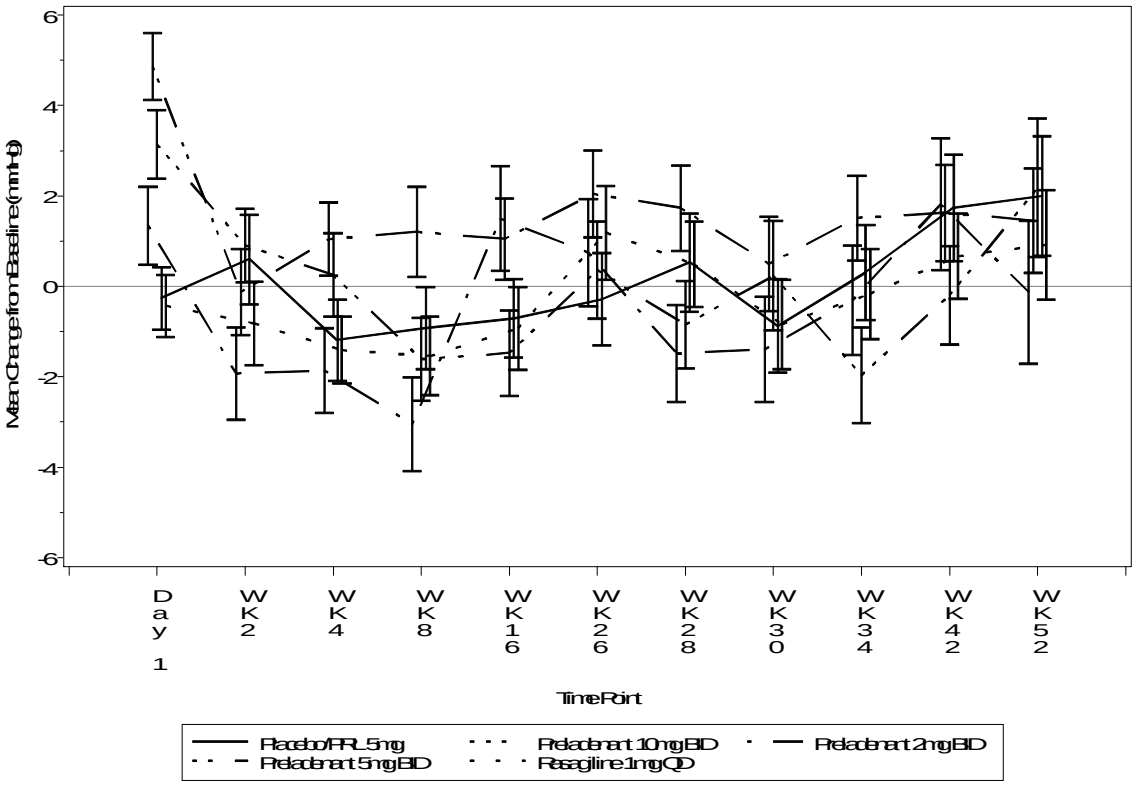
| Treatment | N | Part 1 | | | | |
|---|---|---|---|---|---|---|
| | | ≤1.5xULN | >1.5-3xULN | >3-5xULN | >5-8xULN | >8xULN |
| PRL 2mg BID | 194 | 187 (96.4%) | 5 (2.6%) | 1 (0.5%) | 1 (0.5%) | 0 |
| PRL 5mg BID | 198 | 189 (95.5%) | 6 (3.0%) | 1 (0.5%) | 0 | 2 (1.0%) |
| PRL 10mg BID | 196 | 175 (89.3%) | 12 (6.1%) | 6 (3.1%) | 3 (1.5%) | 0 |
| PBO | 193 | 187 (96.9%) | 6 (3.1%) | 0 | 0 | 0 |
| RAS 1mg QD | 195 | 189 (96.9%) | 3 (1.5%) | 3 (1.5%) | 0 | 0 |
| Treatment | N | Part 2 | | | | |
| | | ≤1.5xULN | >1.5-3xULN | >3-5xULN | >5-8xULN | >8xULN |
| PRL 2mg BID | 165 | 157 (95.2%) | 6 (3.6%) | 2 (1.2%) | 0 | 0 |
| PRL 5mg BID | 173 | 161 (93.1%) | 10 (5.8%) | 2 (1.2%) | 0 | 0 |
| PRL 10mg BID | 164 | 145 (88.4%) | 14 (8.5%) | 4 (2.4%) | 1 (0.6%) | 0 |
| PBO / PRL 5 mg BID | 175 | 164 (93.7%) | 10 (5.7%) | 0 | 1 (0.6%) | 0 |
| RAS 1mg QD | 181 | 170 (93.9%) | 7 (3.9%) | 3 (1.7%) | 0 | 1 (0.6%) |

[redacted]

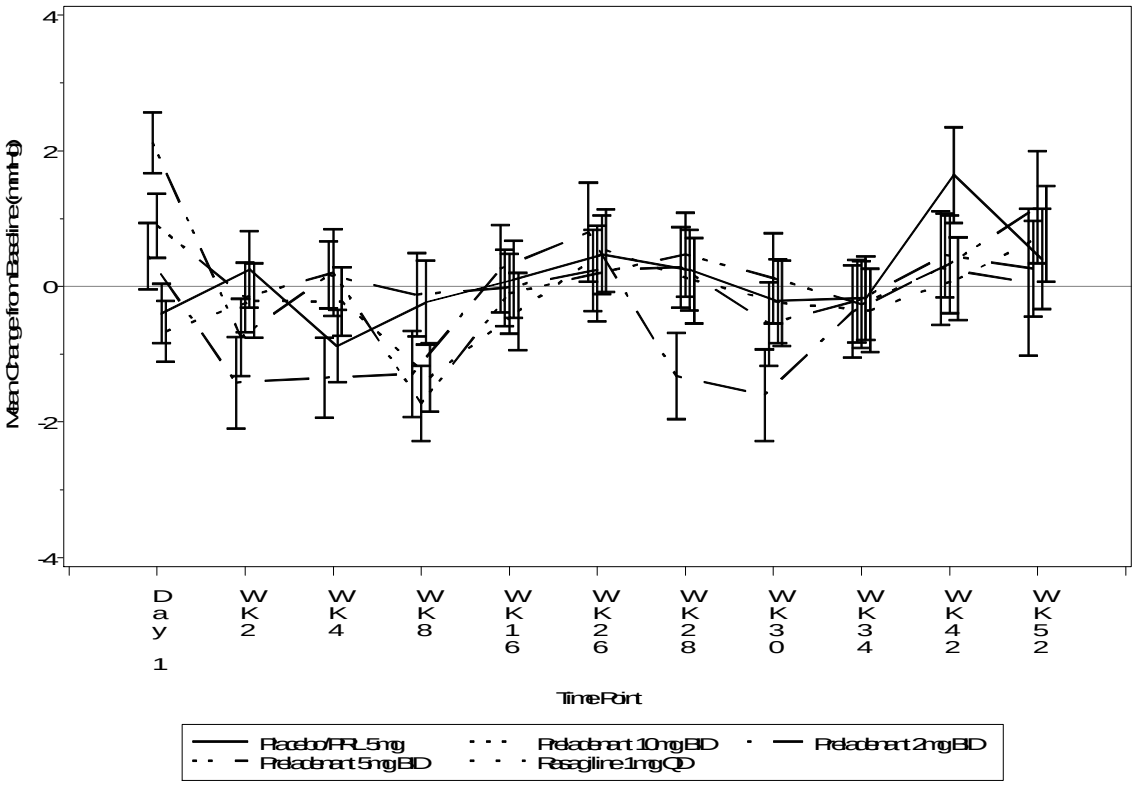
Figures of mean changes in supine BP across the entire study duration are provided below. There were no notable differences in BP among the treatment arms. There was a Day 1 increase of approximately 1.5-5 mmHg in the preladenant groups vs. placebo in supine systolic BP but there were no consistent differences at later time points. Similarly, an average increase of approximately 1-2.5 mmHg in the preladenant 2, 5 and 10mg BID groups vs. placebo was observed on Day 1in supine diastolic BP with no consistent differences at later time points.

Rates of categorical changes from Part 1 study baseline (increases and decreases of >20 mmHg and >40 mmHg in systolic BP and >10 mmHg and >20 mmHg in diastolic BP) were summarized by treatment arm for each time point and for the largest change. Similar rates of categorical changes in supine and standing BP occurred among all treatment arms (data not shown).

Mean Change from Baseline in Supine Systolic Blood Pressure (mmHg) Over Time
Mean Change +/- SE by Treatment Group
(All Subjects As Treated)



Mean Change from Baseline in Supine Diastolic Blood Pressure (mmHg) Over Time
Mean Change +/- SE by Treatment Group
(All Subjects As Treated)




Confidential

| | |
|---|---|
| **CONCLUSIONS:** | This study with placebo and active controls is a failed study. None of the preladenant treatment group demonstrated a statistically significant or clinically meaningful difference vs. placebo at the Week 26 time point in the primary and key secondary efficacy endpoints.<br>• Preladenant was generally well tolerated in this trial.<br>• There were no marked differences in the rates of various types of AEs among the treatment groups. Discontinuation rates due to drug related AEs were small (≤ 4%) 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.<br>• Evaluation of the overall hepatic related safety data (AEs and LFTs) revealed that there were no Hy's Law cases. In both Part 1 and 2 of the study preladenant 10mg BID had the highest rate of ALT increases above 1.5xULN; In Part 1 of the study ALT increases > 3xULN were primarily in the preladenant arms; but in Part 2, rates were more similar in the PRL and RAS arms. AST results were similar overall, but had a fewer cases of increased values >3xULN than ALT.<br>• Overall the changes in BP for the preladenant treatment groups were small and similar to the placebo treatment group.<br>• Incidences of insomnia, suicidal ideation and behavior events, changes from baseline in ESS, and incidences of sleep attack were similar and small among all treatment groups [redacted] |
| **PUBLICATION(S):** | None |