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.,** **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, 40-Week, Active-Controlled, Double-Blind, Double Dummy Extension Study of Preladenant in Subjects With Moderate to Severe Parkinson's Disease (Phase 3; Protocol No. P06153)	
TRIAL IDENTIFIERS:	Protocol Number:	3814-025/P06153
	Clinical Phase:	3
	EudraCT Number:	2009-015162-57
	ISRCT number:	
	Other Codes:	
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.** [redacted]	
TRIAL CENTERS:	A total of 220 centers were approved to screen subjects. The trial was conducted at 220 centers in 31 countries (Austria, Argentina, Brazil, Bulgaria, Colombia, Canada, Chile, Croatia, Czech Republic, Finland, France, Germany, Italy, Israel, India, Mexico, Latvia, Lithuania, Netherlands, Peru, Poland, Portugal, Russia, Serbia, South Africa, Spain, Sweden, Turkey, Ukraine, United Kingdom, and United States). [redacted]	

DESIGN:	This was a double-blind, active-controlled, multi-site extension trial of preladenant in subjects with moderate to severe Parkinson's Disease (PD). The study was conducted in conformance with Good Clinical Practices. All subjects in P06153 were on active medication. The active medications in this study were preladenant 2, 5, or 10 mg twice daily or rasagiline 1 mg once daily. The study consisted of a 1 day screening period, 40 weeks of treatment, and a 2 week follow up period. Subjects who received preladenant 2, 5, or 10 mg twice daily or rasagiline 1 mg once daily in the parent study (P04938 or P07037), continued to receive the same dose and treatment in P06153. Subjects who received placebo in P04938 or P07037 were randomized in a 1:1 ratio to receive preladenant 5 mg twice daily or rasagiline 1 mg once daily in P06153. For additional information about trial design, see the protocol [redacted]. Sample case report forms are not required for a non-submission aCSR. [redacted]	
	Planned duration of main phase: Planned duration of run-in phase: Planned duration of extension phase:	42 weeks (40 weeks of active treatment followed by a 2-week Safety Follow-Up Visit) not applicable not applicable
Objectives	**Primary**: To assess the long-term safety and tolerability of preladenant in subjects with moderate to severe Parkinson's disease (PD). **Secondary**: To characterize the long-term efficacy of preladenant in subjects with moderate to severe PD.	
Hypotheses	Not applicable, this trial was not a hypothesis-testing trial.	
Treatment groups	Preladenant 2 mg BID	Preladenant, 40 weeks, 2mg tablet, administered BID once in morning and again 8 hours later, 218 subjects
	Preladenant 5 mg BID	Preladenant, 40 weeks, 5mg tablet, administered BID once in morning and again 8 hours later, 215 subjects
	Placebo/Preladenant 5 mg BID	Preladenant, 40 weeks, (on placebo in parent study) 5mg tablet, administered BID once in morning and again 8 hours later, 106 subjects

	Preladenant 10 mg BID	Preladenant, 40 weeks, 10mg tablet, administered BID once in morning and again 8 hours later, 96 subjects
	Rasagiline 1 mg QD	Rasagiline, 40 weeks, 1mg capsule, administered QD once in morning, 93 subjects
	Placebo/Rasagiline 1 mg QD	Rasagiline, 40 weeks, (on placebo in parent study), 1mg capsule, administered QD once in morning, 108 subjects

Clinical Supplies Table

Clinical Material	Potency	Form/Packaging	Batch Numbers
Preladenant	2 mg	Tablet	[redacted]
Preladenant	5 mg	Tablet	
Preladenant	10 mg	Tablet	
Rasagiline	1 mg	Capsule	
Placebo	NA	Capsule	
Placebo	NA	Tablet	

Endpoints and definitions	Safety		Safety assessments included adverse events (AEs), serious adverse events (SAEs), laboratory safety tests including liver related enzymes, 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).

	Prespecified safety endpoints		The incidences of systolic blood pressure ≥ 180 mm Hg, diastolic blood pressure ≥ 105 mm Hg, ALT ≥ 3X ULN and ≥ 10% increase from Baseline, AST ≥ 3X ULN and ≥ 10% increase from Baseline, Suicidality as measured by C-SSRS, and Epworth Sleepiness Scale score.
	Efficacy		MoCA score, EQ-5D score, PDQ-39 score, BDI-II score, Apathy Scale score; the following diary data: mean hours per day spent in the "off" state, mean hours per day spent in the "on" state, mean hours per day spent in the "on" state without troublesome dyskinesias, mean hours per day spent in the "on" state with troublesome dyskinesias, proportion of "on" time with and without troublesome dyskinesias, proportion of "on" time with no dyskinesias, mean total sleep time, 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.
Database lock	26-AUG-2013	Trial status	23-NOV-2010 first subject first visit to 16-JUL-2013 last subject last visit (trial terminated early)
RESULTS AND ANALYSIS:	All analyses for safety were performed according to the protocol [redacted] Due to the early termination of the trial, efficacy analyses were limited to descriptive statistics.		

Analysis description	**Primary Analysis**
Analysis population and time point description	All Subjects as Treated (ASaT) Set: All subjects who received at least one dose of study drug in P06153. The safety assessment was conducted utilizing the ASaT set. In the safety assessment, subjects were analyzed according to the treatment actually received. Adverse Event Summaries included all observed AE's during the 40 Week trial and 30 days post-treatment period.
Summary	Descriptive statistics were used to assess long-term safety. Summary statistics (mean, standard deviation, median, minimum and maximum) were provided for continuous variables including observed values and changes from Baseline. Baseline values for safety endpoints were taken from the last observed value prior to administration of study treatment in the parent study. Analyses of AE's of interest including the incidence of elevated BP [systolic ≥180 mm Hg and/or diastolic ≥105 mm Hg], elevated liver related enzymes [ALT and/or AST ≥3 x ULN with a ≥10% increase from Baseline], and suicidality incidence were performed using the Clopper Pearson Exact Method. The 95% exact confidence intervals for each of the doses have been provided. Listings of safety data provided and values outside the normal range were flagged, where applicable.
Analysis description	Efficacy Analysis
Analysis population and time point description	Analysis Set (FAS): All randomized subjects were used for analysis. Visits were at Baseline, Week 2, Week 4, Week 6, Week 8, Week 12, Week 16, Week 20, 24, 28, 32, 36, and 40 for efficacy analysis depending upon visit scheduling. [redacted]
Summary	Summary statistics for efficacy (mean, standard deviation, median, minimum and maximum) and 95% CI were provided for continuous variables including observed values and changes from baseline. Baseline for Diary endpoints were derived from the available diary data collected for 3 days prior to Randomization in the parent study (P04938 or P07037). Baseline values for other efficacy endpoints were taken from the last observed value prior to administration of study treatment in the parent study.

ANALYSIS RESULTS:

A total of 839 subjects were randomized and of those 836 subjects were treated in this study; 485 subjects (58%) came from the P04938 study and 351 subjects (42%) came from the P07037 study. This study was stopped early due to the lack of efficacy of preladenant in the parent studies. At the time of stopping, 387 (46%) of subjects had completed the 40-week trial. A tabular presentation of disposition is provided on the next page [redacted].

A total of 11 (5%) subjects in the PRL 2 mg BID group, 11 (5%) subjects in the PRL 5 mg BID group, 4 (4%) subjects in the placebo/PRL 5 mg BID group, 8 (8%) of subjects in the 10 mg BID group, 7 (8%) in the rasagiline 1 mg QD group, and 6 (6%) in the placebo/ rasagiline 1 mg QD group were discontinued due to an AE. There were 12 subjects discontinued from the trial because of an SAE: 2 (1%) subjects in the PRL 2 mg BID group, 2 (1%) subjects in the PRL 5 mg BID group, 1 (1%) subject in the placebo/PRL 5 mg BID group, 5 (5%) of subjects in the 10 mg BID group, 1 (1%) in the rasagiline 1 mg QD group, and 1 (1%) in the placebo/ rasagiline 1 mg QD group. [redacted]. Reasons for discontinuation after administration of trial medication are shown in the subject disposition table; [redacted].

All Treated Subjects
Subject Disposition – Treatment Phase

	PRL 2 mg BID	PRL 5 mg BID	PLA/PRL 5 mg BID	PRL 10 mg BID	All PRL	RAS 1 mg QD	PLA/RAS 1mg QD	All RAS
Treated	218 (100)	215 (100)	106 (100)	96 (100)	635 (100)	93 (100)	108 (100)	201 (100)
Discontinued Treatment Phase	121 (56)	118 (55)	56 (53)	48 (50)	343 (54)	48 (52)	57 (53)	105 (52)
Adverse Event	11 (5)	11 (5)	4 (4)	8 (8)	34 (5)	7 (8)	6 (6)	13 (6)
Treatment Failure	8 (4)	4 (2)	1 (1)	5 (5)	18 (3)	1 (1)	1 (1)	2 (1)
Lost To Follow-Up	1 (<1)	4 (2)	1 (1)	1 (1)	7 (1)	1 (1)	2 (2)	3 (1)
Subject Withdrew Consent	16 (7)	20 (9)	7 (7)	10 (10)	53 (8)	11 (12)	8 (7)	19 (9)
Non-Compliance With Protocol	2 (1)	6 (3)	1 (1)	0	9 (1)	0	0	0
Administrative	83 (38)	73 (34)	42 (40)	24 (25)	222 (35)	28 30)	40 (37)	68 (34)
Completed Treatment Phase	97 (44)	96 (45)	50 (47)	48 (50)	291 (46)	45 48)	51 (47)	96 (48)
Missing Status	0	1 (<1)	0	0	1 (<1)	0	0	0

[redacted]

Overall, baseline demographics and disease characteristics were similar among the treatment groups. More male subjects were randomized in each treatment group with the exception of the PLA/PRL 5 mg BID treatment group (48% male). The mean age of subjects was 62.4, 63.0, 64.4, 63.9, 63.8, and 63.9 years for the PRL 2 mg BID, PRL 5 mg BID, PLA/PRL 5 mg BID, PRL 10 mg BID, RAS 1 mg QD and PLA/RAS 1 mg QD treatment groups respectively, with an overall age range of 33 to 84 years. The mean daily L Dopa dose was 858.9, 799.5, 748.5, 827.0, 1097.3, and 900.5 mg for the PRL 2 mg BID, PRL 5 mg BID, PLA/PRL 5 mg BID, PRL 10 mg BID, RAS 1 mg QD and PLA/RAS 1 mg QD treatment groups respectively. The overall range for daily L Dopa dose was 57.0-5250.0 mg.

All Treated Subjects
Summary of Demographics and Baseline Characteristics

	PRL 2 mg BID n=218	PRL 5 mg BID n=215	PLA/PRL 5 mg BID n=106	PRL 10 mg BID n=96	RAS 1 mg QD n=93	PLA/RAS 1mg QD n=108	Total n=836
Sex (n,%)							
Female	68 (31)	100 (47)	55 (52)	40 (42)	37 (40)	41 (38)	341 (41)
Male	150 (69)	115 (53)	51 (48)	56 (58)	56 (60)	67 (62)	495 (59)
Race (n,%)							
White	198 (91)	195 (91)	91 (86)	86 (90)	82 (88)	98 (91)	750 (90)
Non-White	20 (9)	20 (9)	15 (14)	10 (10)	11 (12)	10 (9)	86 (10)
Asian	6 (3)	2 (1)	2 (2)	3 (3)	1 (1)	5 (5)	19 (2)
Black or African American	0	2 (1)	1 (1)	0	0	0	3 (<1)
Multiracial	14 (6)	16 (7)	12 (11)	7 (7)	10 (11)	5 (5)	64 (8)
Ethnicity (n,%)							
Hispanic or Latino	56 (26)	43 (20)	28 (26)	12 (13)	23 (25)	15 (14)	177 (21)
Not Hispanic or Latino	162 (74)	172 (80)	78 (74)	84 (88)	70 (75)	93 (86)	659 (79)
Age (yrs)							
Mean (SD)	62.4 (8.5)	63.0 (8.7)	64.4 (8.7)	63.9 (8.0)	63.8 (9.9)	63.9 (7.8)	63.3 (8.6)
Median	62.0	64.0	65.5	65.0	63.0	63.0	63.5
Range	33 - 84	38 - 84	34 - 79	41 - 79	36 - 83	46 - 82	33 - 84
Age (n,%)							
30 - <55	37 (17)	37 (17)	15 (14)	11 (11)	19 (20)	11 (10)	130 (16)
55 - <65	95 (44)	82 (38)	34 (32)	34 (35)	31 (33)	53 (49)	329 (39)
65 - <75	71 (33)	78 (36)	49 (46)	42 (44)	28 (30)	34 (31)	302 (36)

	PRL 2 mg BID n=218	PRL 5 mg BID n=215	PLA/PRL 5 mg BID n=106	PRL 10 mg BID n=96	RAS 1 mg QD n=93	PLA/RAS 1mg QD n=108	Total n=836
>=75	15 (7)	18 (8)	8 (8)	9 (9)	15 (16)	10 (9)	75 (9)
Weight (kg)							
Mean (SD)	76.65 (15.46)	76.12 (15.89)	69.71 (14.22)	73.79 (14.46)	74.91 (15.77)	75.66 (18.44)	74.99 (15.87)
Median	76.11	75.00	69.00	73.72	72.00	74.00	74.00
Range	34.5 - 120.0	44.2 - 129.8	40.0 - 119.8	36.7 - 115.0	46.2 - 118.1	36.3 - 148.9	34.5 - 148.9
Missing	0	5	3	0	0	0	8
Height (cm)							
Mean (SD)	170.02 (9.91)	169.02 (10.28)	165.42 (9.41)	168.62 (9.08)	168.32 (9.74)	167.31 (10.35)	168.49 (9.97)
Median	170.18	170.00	164.10	168.75	169.00	166.25	168.00
Range	143.0 - 193.0	142.7 - 190.0	141.0 - 195.6	147.3 - 192.0	148.0 - 188.0	143.0 - 189.0	141.0 - 195.6
Missing	1	4	4	0	1	0	10
Total Daily L-Dopa dose(mg)							
Mean (SD)	858.9 (490.4)	799.5 (521.8)	748.5 (445.0)	827.0 (540.4)	1097.3 (810.6)	900.5 (593.5)	858.0 (563.3)
Median	750.0	650.0	625.0	687.5	800.0	750.0	750.0
Range	150.0 - 3000.0	125.0 - 3600.0	125.0 - 2400.0	200.0 - 3600.0	200.0 - 5250.0	57.0 - 4000.0	57.0 - 5250.0
Missing	1	1	0	2	0	0	4

[redacted]

The clinical adverse experience summary table presents an overview of the number and percentage of subjects with AEs, according to types of AEs. A total of 836 patients were treated. The incidence of AEs was similar across the treatment arms. Of subjects treated, 133 (66%) of RAS vs. 402 (63%) of PRL experienced one or more adverse events. Discontinuations due to drug related AEs were lower in the PRL treated subjects (22 [3%]) compared to the RAS treated subjects (8[4%]). There was a higher percentage of subjects with serious adverse events in the PRL 10 mg BID treatment group (12 [13%)] vs. the PRL 2 mg BID, PRL 5 mg BID, and PLA/PRL 5 mg BID groups (11 [5%], 15 [7%], 6 [6%]). Similarly, there was a higher percentage of subjects with serious drug related adverse events in the PRL 10 mg BID treatment group (5 [5%)] vs. the PRL 2 mg BID, PRL 5 mg BID, and PLA/PRL 5 mg BID groups (5 [2%], 4 [2%], 1 [1%]). The overall discontinuation rate due to serious drug related AEs was 1% for all treatment groups within the study with the exception of the PRL 10 mg BID treatment group (3[3%]).

All Treated Subjects
Clinical Adverse Experiences Summary

	Number of Subjects (%)															
	PRL 2 mg BID n=218		PRL 5 mg BID n=215		PLA/PRL 5 mg BID n=106		PRL 10 mg BID n=96		All PRL n=635		RAS 1 mg QD n=93		PLA/RAS 1mg QD n=108		All RAS n=201	
Number (%) of subjects with:																
One or more adverse events	138	(63)	134	(62)	69	(65)	61	(64)	402	(63)	62	(67)	71	(66)	133	(66)
Drug-related adverse events[1]	74	(34)	80	(37)	35	(33)	31	(32)	220	(35)	31	(33)	39	(36)	70	(35)
Serious adverse events[2]	11	(5)	15	(7)	6	(6)	12	(13)	44	(7)	5	(5)	4	(4)	9	(4)
Serious drug-related adverse events	5	(2)	4	(2)	1	(1)	5	(5)	15	(2)	2	(2)	0		2	(1)
Death	0		1	(<1)	1	(1)	2	(2)	4	(1)	1	(1)	1	(1)	2	(1)
Discontinuation due to adverse event	9	(4)	10	(5)	4	(4)	8	(8)	31	(5)	6	(6)	6	(6)	12	(6)
Discontinuation due to drug-related adverse event	8	(4)	7	(3)	2	(2)	5	(5)	22	(3)	5	(5)	3	(3)	8	(4)
Discontinuation due to serious adverse event	2	(1)	2	(1)	1	(1)	5	(5)	10	(2)	1	(1)	1	(1)	2	(1)
Discontinuation due to serious drug-related adverse event	1	(<1)	0		0		3	(3)	4	(1)	1	(1)	0		1	(<1)

1: Determined by the investigator to be possibly, probably, or definitely drug-related.
2: All serious adverse events are reported, regardless of treatment emergence.
Every subject is counted a single time for each applicable specific adverse event.
[redacted]

The adverse events with the highest incidence rates for all preladenant groups combined were (in order starting from highest incidence): dyskinesia (42[7%]), constipation (33[5%]), Parkinson's Disease (33[5%]), fall (32[5%]), and urinary tract infection (31[5%]). There was generally no dose dependent increased incidence of AEs. The only exceptions were arthralgia, tremor, fatigue, and blood creatine phosphokinase increased. For these events, the incidence was highest in the PRL 10mg BID group compared to the other treatment groups (table below).

All Treated Subjects
Summary of Treatment Emergent Adverse Events (5% Incidence)
Number (%) of Subjects

	PRL 2 mg BID n=218	PRL 5 mg BID n=215	PLA/PRL 5 mg BID n=106	PRL 10 mg BID n=96	All PRL n=635	RAS 1 mg QD n=93	PLA/RAS 1mg QD n=108	All RAS n=201
SUBJECTS REPORTING ANY ADVERSE EVENT	138 (63)	134 (62)	69 (65)	61 (64)	402 (63)	62 (67)	71 (66)	133 (66)
Gastrointestinal Disorders								
Constipation	9 (4)	12 (6)	7 (7)	5 (5)	33 (5)	1 (1)	3 (3)	4 (2)
Nausea	6 (3)	8 (4)	3 (3)	1 (1)	18 (3)	2 (2)	7 (6)	9 (4)
General Disorders And Administration Site Conditions								
Fatigue	7 (3)	6 (3)	3 (3)	5 (5)	21 (3)	0	2 (2)	2 (1)
Infections And Infestations								
Nasopharyngitis	12 (6)	7 (3)	3 (3)	2 (2)	24 (4)	4 (4)	7 (6)	11 (5)
Urinary Tract Infection	10 (5)	10 (5)	6 (6)	5 (5)	31 (5)	2 (2)	6 (6)	8 (4)
Injury, Poisoning And Procedural Complications								
Fall	7 (3)	16 (7)	5 (5)	4 (4)	32 (5)	3 (3)	4 (4)	7 (3)
Investigations								
Blood Creatine Phosphokinase Increased	7 (3)	4 (2)	1 (1)	5 (5)	17 (3)	3 (3)	1 (1)	4 (2)
Weight Decreased	1 (<1)	2 (1)	0	1 (1)	4 (1)	5 (5)	2 (2)	7 (3)
Musculoskeletal And Connective Tissue Disorders								
Arthralgia	3 (1)	2 (1)	0	5 (5)	10 (2)	2 (2)	9 (8)	11 (5)
Back Pain	5 (2)	7 (3)	7 (7)	1 (1)	20 (3)	3 (3)	5 (5)	8 (4)

	PRL 2 mg BID n=218	PRL 5 mg BID n=215	PLA/PRL 5 mg BID n=106	PRL 10 mg BID n=96	All PRL n=635	RAS 1 mg QD n=93	PLA/RAS 1mg QD n=108	All RAS n=201
Nervous System Disorders								
Dizziness	9 (4)	7 (3)	5 (5)	1 (1)	22 (3)	1 (1)	5 (5)	6 (3)
Dyskinesia	10 (5)	19 (9)	5 (5)	8 (8)	42 (7)	8 (9)	9 (8)	17 (8)
Headache	7 (3)	10 (5)	4 (4)	4 (4)	25 (4)	4 (4)	5 (5)	9 (4)
Parkinson's Disease	11 (5)	13 (6)	4 (4)	5 (5)	33 (5)	3 (3)	0	3 (1)
Tremor	5 (2)	2 (1)	1 (1)	5 (5)	13 (2)	0	1 (1)	1 (<1)
Psychiatric Disorders								
Depression	5 (2)	5 (2)	5 (5)	2 (2)	17 (3)	1 (1)	2 (2)	3 (1)
Hallucination	1 (<1)	2 (1)	5 (5)	1 (1)	9 (1)	1 (1)	1 (1)	2 (1)

Note: % incidence is based on meeting the criteria in any Treatment Arm.

[redacted]

There were six deaths in P06153:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

ALT/AST:

There were 13 subjects in this study with events of ALT or AST ≥3x ULN and ≥10% increase from baseline. One of the 13 subjects had two elevations. Overall, the rates of ALT elevations ≥3x ULN were low (~1%) and similar among preladenant and rasagiline-treated subjects; however, the highest elevations (>5xULN) occurred only in the preladenant arms. Results for AST showed a lower rate of elevations for preladenant -treated subjects [3 of 561 (0.5%)] compared with 4 of 175 (2.3%) rasagiline-treated subjects as summarized in the table below.

[redacted] This event was determined by the adjudication committee to be unrelated to study medication. The committee identified a confounder of acute infectious mononucleosis.

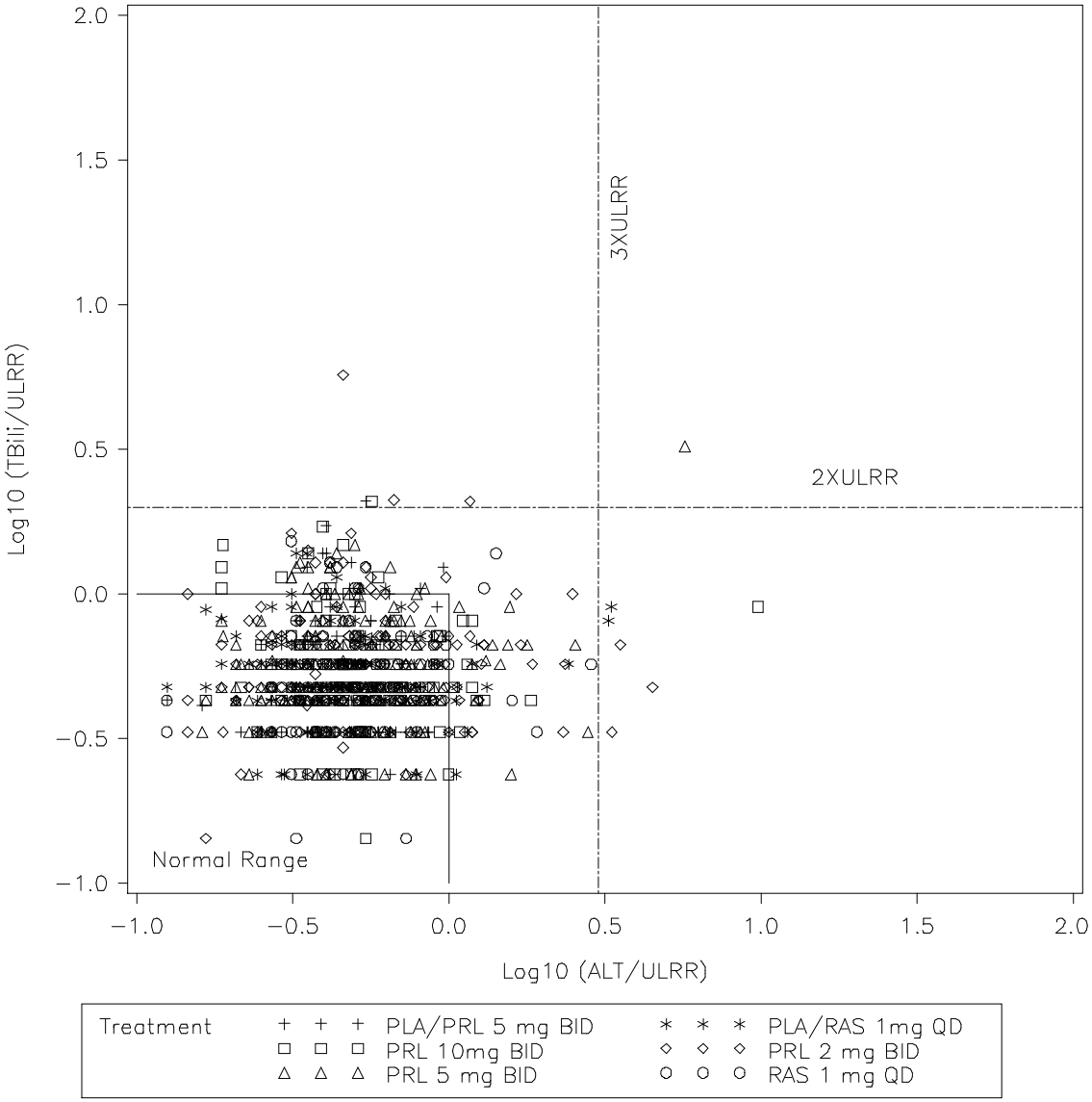
A cross check was done for the 13 subjects in P06153 with ALT/AST elevations ≥ 3X ULN and ≥ 10% above baseline to see if any of the subjects had experienced a similar elevation in the parent study. One subject was identified. [redacted]

Incidence of Categorical Change in ALT – Highest Result						
Treatment	**N**	**≤1.5xULN**	**>1.5-3xULN**	**>3-5xULN**	**>5-8xULN**	**>8xULN**
PRL 2mg BID	189	183 (96.8%)	3 (1.6%)	3 (1.6%)	0	0
PRL 5mg BID	195	190 (97.4%)	4 (2.1%)	0	1 (0.5%)	0
PBO / PRL 5 mg BID	93	93 (100%)	0	0	0	0
PRL 10mg BID	80	78 (97.5%)	1 (1.3%)	0	0	1 (1.3%)
RAS 1mg QD	80	78 (97.5%)	2 (2.5%)	0	0	0
PBO / RAS 1 mg QD	97	95 (97.9%)	0	2 (2.1%)	0	0
Incidence of Categorical Change in AST – Highest Result						
Treatment	**N**	**≤1.5xULN**	**>1.5-3xULN**	**>3-5xULN**	**>5-8xULN**	**>8xULN**
PRL 2mg BID	190	187 (98.4%)	1 (0.5%)	2 (1.1%)	0	0
PRL 5mg BID	198	196 (99%)	2 (1%)	0	0	0
PBO / PRL 5 mg BID	91	90 (98.9%)	1 (1.1%)	0	0	0
PRL 10mg BID	82	80 (97.6%)	1 (1.2%)	0	1 (1.2%)	0
RAS 1mg QD	79	77 (97.5%)	1 (1.3%)	1 (1.3%)	0	0
PBO / RAS 1 mg QD	96	92 (95.8%)	1 (1%)	2 (2.1%)	0	1 (1%)

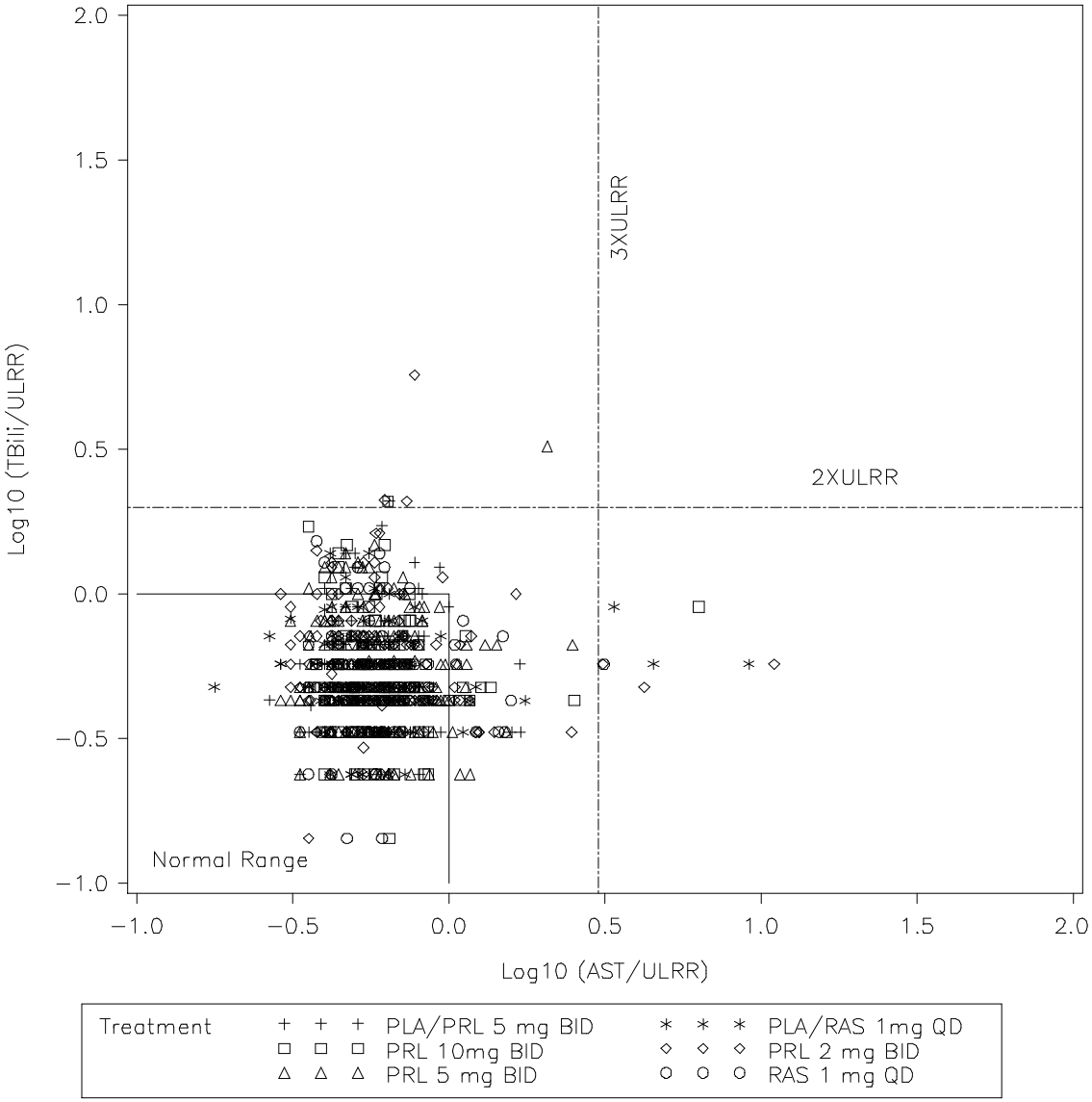
Source: C44114; C44214

The figures below are scatter plots showing the highest level of ALT or AST and total bilirubin for each subject in P06153.

Maximum On-treatment Total Bilirubin and ALT (SGPT)
by Treatment Group
(All Subjects As Treated)



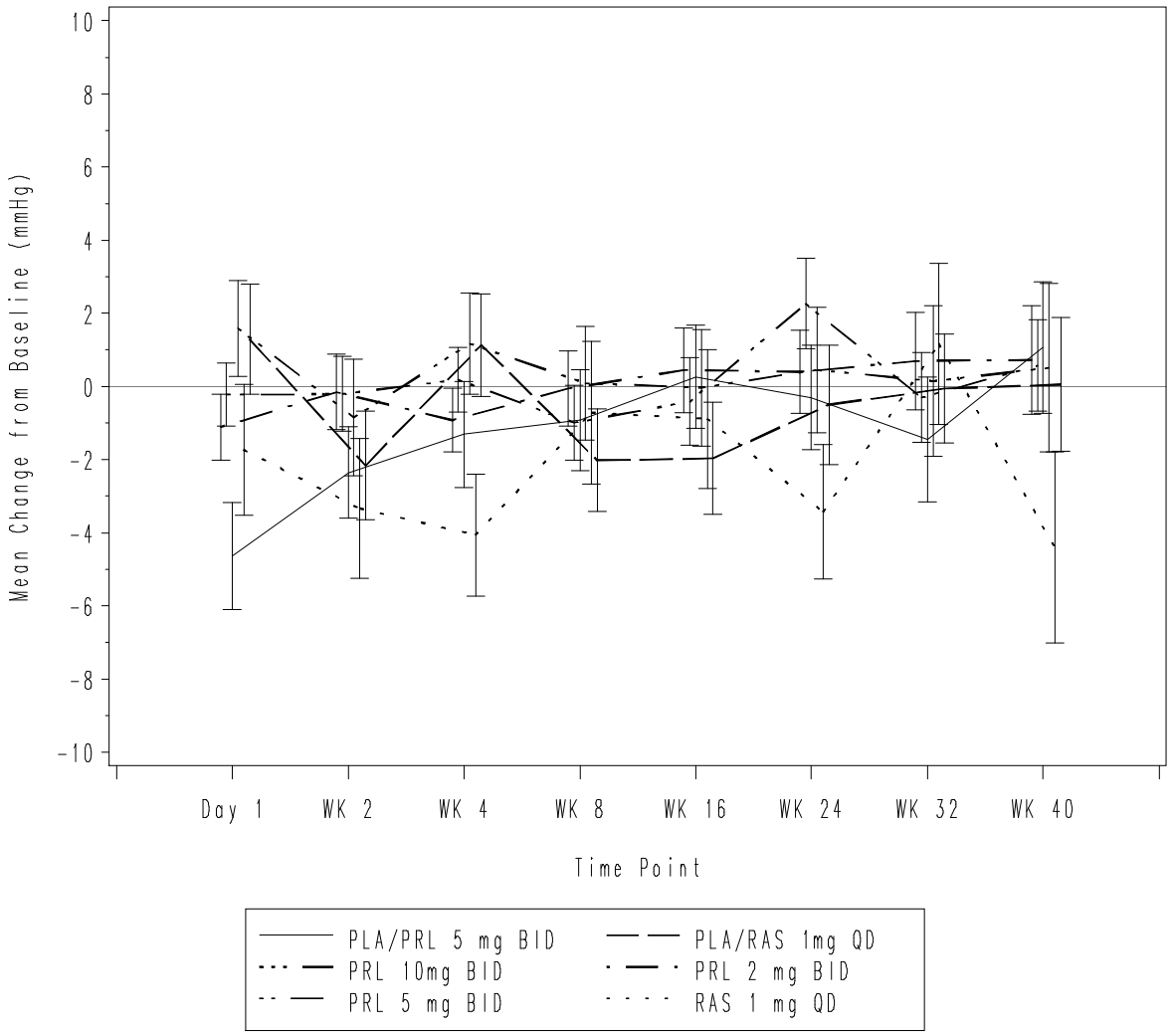
Maximum On-treatment Total Bilirubin and AST (SGOT)
by Treatment Group
(All Subjects as Treated)



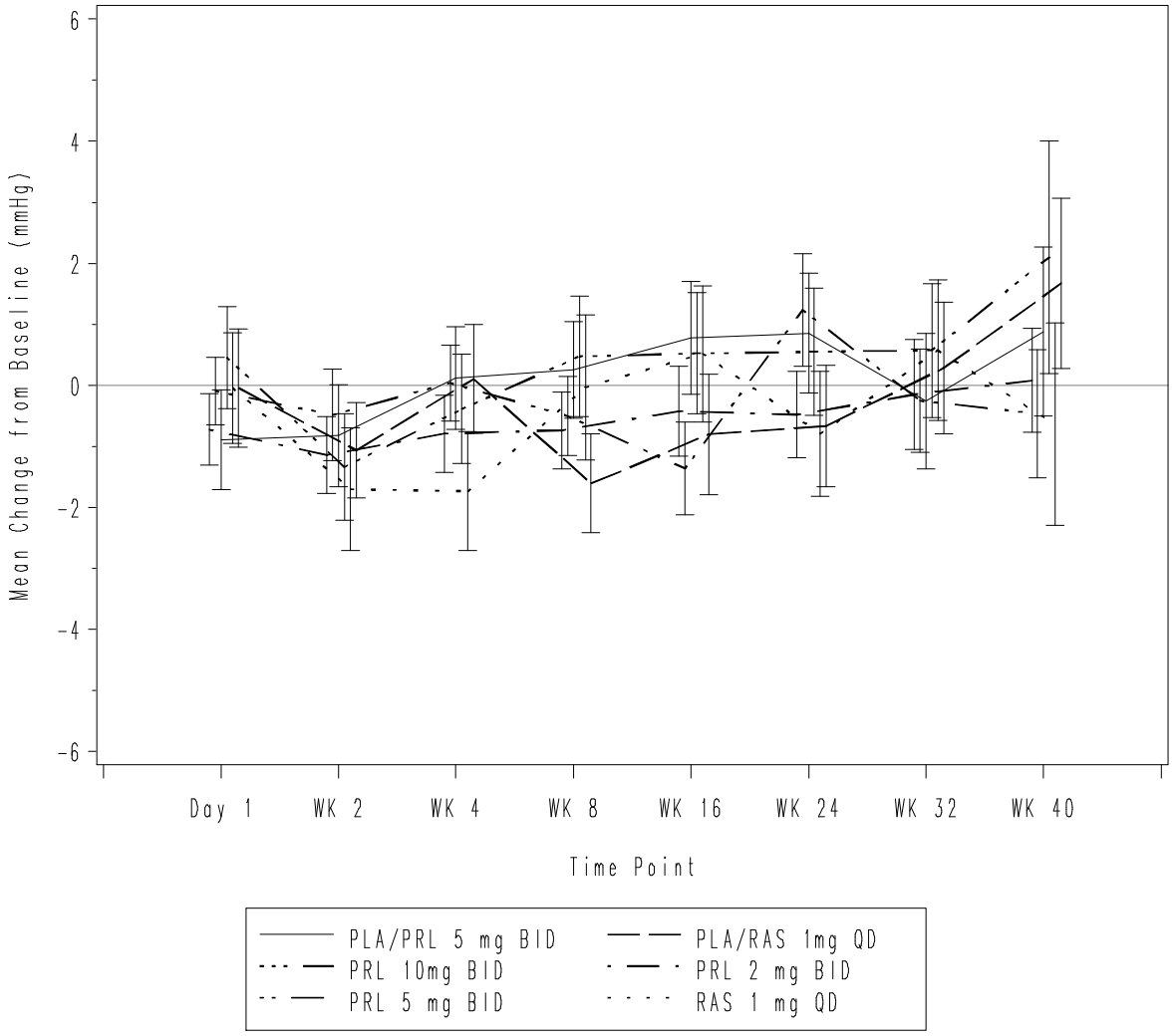
Supine Systolic and Diastolic BP:

Changes from the parent studies' baseline supine systolic blood pressure were generally small and not different among treatment arms. One exception was the Day 1 placebo/ preladenant 5 mg BID group where the Day 1 values reflect the end-of-parent study treatment (placebo) and the Week 2 and beyond values reflect the extension study treatment (preladenant 5 mg BID). The rasagiline group had wider changes and greater variability in blood pressure during the 40 week treatment period. In this treatment group, the systolic BP dropped during the parent study and returned to baseline values during the extension phase of the trial.

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)



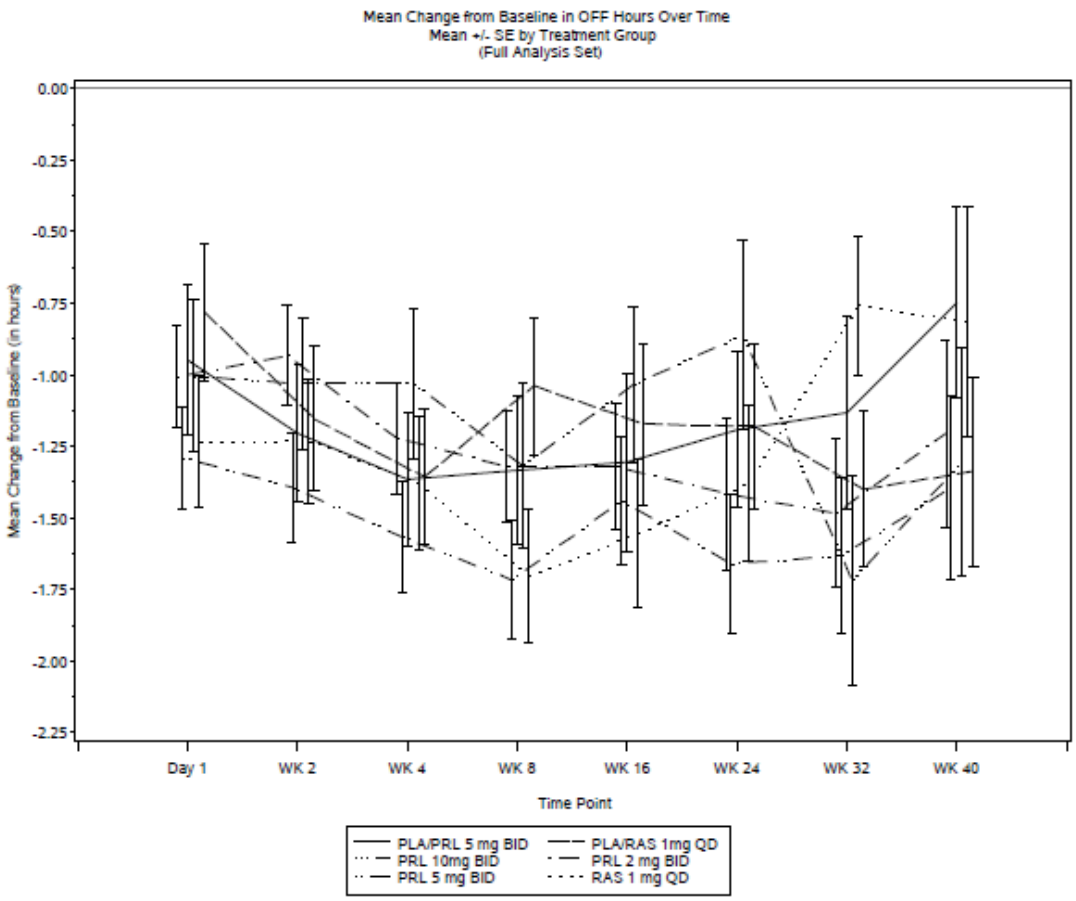
Other Safety Endpoints:

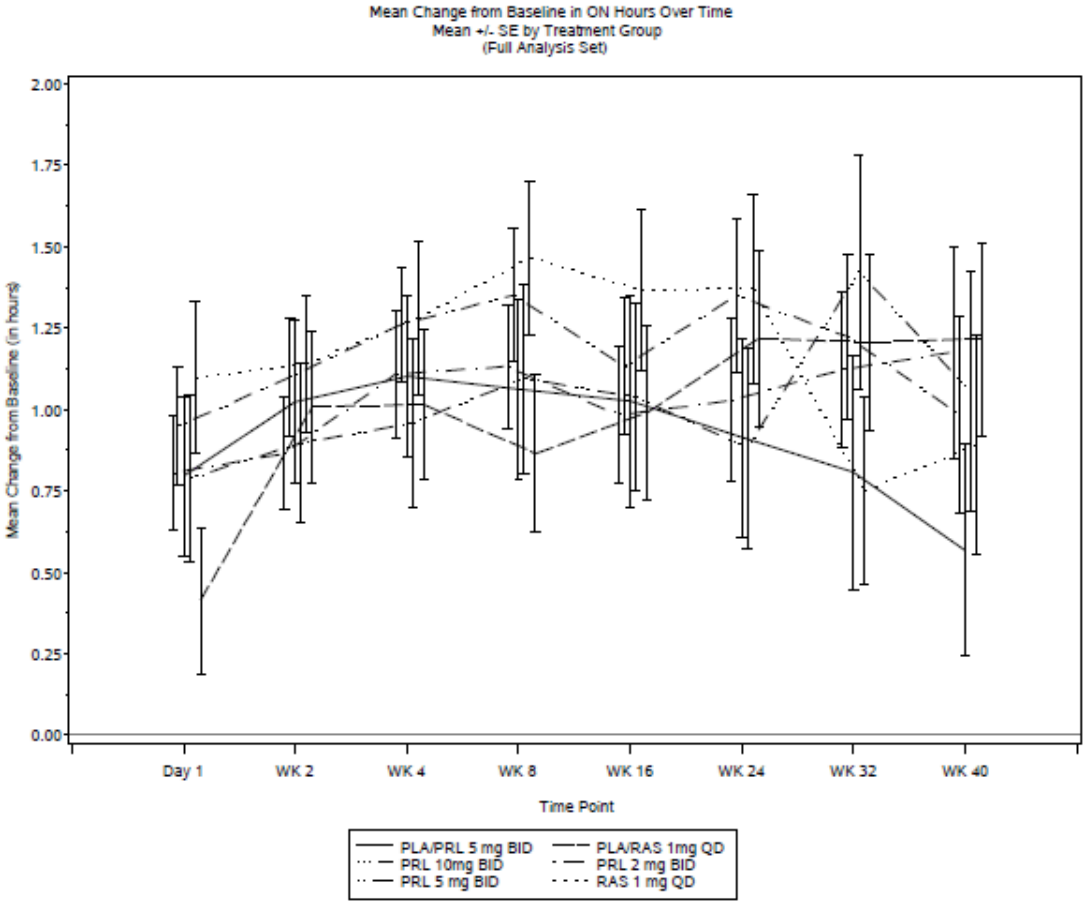
- Changes from baseline in Columbia-Suicide Severity Rating Scale (C-SSRS) showed majority of subjects did not have events of suicidal ideation and behavior, ≥93% of the subjects across treatment arms. The highest incidence of suicidal ideation or behavior was observed in the preladenant 5 mg BID arm (6%). There were no differences between other treatment arms (≤4%).
- Change from baseline in Epworth sleepiness scale score and change from baseline in Questionnaire for Impulsive-Compulsive Disorders in PD – Rating Scale (QUIP-RS) Total Score at week 40, did not show variation in magnitude between treatment arms.
- Sleep attack, there were <4% subjects had >2 sleep attacks at Week 40. The highest incidence was observed in the preladenant 5 mg BID arm (4%). There were no differences between other treatment arms (≤3%).

Efficacy Results:

The figures below show the efficacy endpoints. Note that due to stopping the study early, there were fewer subjects providing data at the later time points. Therefore results should be viewed with caution. Note that changes are reflective of changes from the parent study baseline. Baseline for diary endpoints were derived from the available diary data collected for 3 days prior to randomization in the parent study (P04938 or P07037). Baseline for the other efficacy endpoints listed below was taken from the last observed value prior to administration of study treatment in the parent study.

- Change from baseline in mean hours per day spent in the "off" state, by treatment groups and week: Average "off" time decreases ranged from approximately 0.75 hours to 1.5 hours across the 40 weeks; as with the parent study data there is no evidence of a preladenant dose response. Subjects treated with preladenant 5mg BID throughout the parent and extension studies had the largest decrease in "off" time among the treatment arms during the first 8 weeks of the study.
- Change from baseline in mean hours per day spent in the "on" state, by treatment groups and week: Average "on" time increases ranged from approximately 0.75 hours to 1.5 hours across the 40 weeks. As with the parent study data there is no evidence of a preladenant dose response. Subjects treated with rasagiline 1 mg QD throughout the parent and extension studies had the largest increase in "on" time among the treatment arms during the first 24 weeks of the study with similar results from subjects who were treated with preladenant 5 mg BID throughout the parent and extension studies.





SUMMARY OF OTHER EFFICACY ENDPOINTS:

Diary Data:

- Change from baseline in mean hours per day spent in the “on” state without troublesome dyskinesias at Week 40 ranged from 0.4 to 1.1 hours/day with largest increase in Placebo/ preladenant 5mg BID arm from 9.3 hours/day at baseline to 10.2 hours/day at Week 40.
- Change from baseline in mean hours per day spent in the “on” state with troublesome dyskinesias at Week 40 ranged from -0.1 to 0.2 hours/day with decrease in rasagiline 1 mg QD arm.
- There were no changes observed in proportion of “on” time with no dyskinesias, proportion of “on” time without troublesome dyskinesias, and proportion of “on” time with troublesome dyskinesias;
- Change from baseline in mean total sleep time had minimal amount of increase ranged from 0-0.4 hours/day across treatment groups. Preladenant 5mg BID arm had the largest increase 0.4 hours/day at Week 40.

Total Unified Parkinson's Disease Rating Scale (UPDRS) Score in the "on" state:

- Change from baseline in UPDRS score for Parts 1, 2, and 3 combined and Parts 2 and 3 combined showed a similar trend. Decreases from baseline in the range of (-6.4, -2.7) and (-6.6, -2.8) respectively were observed. The largest decrease in magnitude was observed in Placebo/ rasagiline 1 mg QD arm in both endpoints.
- Change from baseline in UPDRS subscale scores for Parts 1, 2, 3 and 4 showed a similar trend. The largest decrease from baseline was observed in the Part 3 endpoint (-5.9, -2.9) with Placebo/ rasagiline 1 mg QD arm having the largest decrease.
- Change from baseline in Tremor domain of UPDRS Part 3 showed decreases from baseline in the range of (-1.1,-0.4). The rasagiline 1 mg QD arm had the largest decrease.

Other efficacy endpoints:

- Change from baseline in Montreal Cognitive Assessment (MoCA) score was similar between treatment groups at Week 40. The largest decrease was observed in the Placebo/ rasagiline 1 mg QD arm.
- There were no changes from baseline observed for EuroQol Five Dimension Questionnaire (EQ-5D) index score at Week 40.
- Change from baseline in EQ-5D VAS score ranged from (-5, 1.4). The largest increase was seen in preladenant 2 mg BID at Week 40.
- Change from baseline in Parkinson's Disease Questionnaire (PDQ-39) at Week 40 ranged from (-0.8, 1.1). The largest increase was seen in the Placebo/ rasagiline 1 mg QD arm at Week 40.
- Changes from baseline in Beck Depression Inventory (BDI-II) score at Week 40 were similarly increased across all treatment groups. The largest increase of 2.1 points was observed in preladenant 10 mg BID at Week 40.
- Changes from baseline in apathy scale score at Week 40 were similarly increased across all treatment groups. The largest increase was observed in Placebo/ rasagiline 1 mg QD arm with 2.1 points.

CONCLUSIONS:	In this 40 week safety extension study to the placebo controlled studies of preladenant in the treatment of patients with moderate to severe PD on stable doses of L-Dopa therapy experiencing motor fluctuations there were no new safety findings observed and preladenant was generally well tolerated. Treatment groups were similar based on demographics including the mean daily dose of L-Dopa. The most common reason for discontinuation from the study was administrative (25-40%) due to early termination of the study due to lack of efficacy in the parent studies. Discontinuation due to adverse events was similar across preladenant treatment groups and similar to the rasagiline group. In the 10 mg BID group there were more SAEs, drug related SAEs and more discontinuations due to serious drug related SAEs. Although the highest elevations in LFTs occurred in the preladenant group, the overall rate was similar across treatment groups. Efficacy results were similar to those observed in the parent studies with no evidence of a dose response across the preladenant groups.