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, 12-Week, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Preladenant in Subjects With Moderate to Severe Parkinson's Disease (Phase 3; Protocol No. P07037)	
TRIAL IDENTIFIERS:	Protocol Number:	3814-028/P07037
	Clinical Phase:	3
	EudraCT Number:	2010-020112-11
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 88 centers were approved to screen subjects. The trial was conducted at 88 centers in 12 countries (Croatia, Latvia, Lithuania, Russia, Serbia, Ukraine, South Africa, Argentenia, Chile, Columbia, Mexico, and United States). [redacted]	
DESIGN:	This was a randomized, placebo controlled, parallel group, multiple center, double blind trial of PRL in adult subjects with moderate to severe Parkinson's disease (PD). Following a Screening Period of up to 5 weeks, subjects were randomized into one of three treatment groups (PRL 2 or PRL 5 mg twice daily (BID) or placebo) in a 1:1:1 ratio and receive double blind treatment for 12 weeks. At the end of the Treatment Period, subjects could choose to enter into the extension trial (up until the maximum number of subjects for that extension trial has been reached) or return for a Follow Up Visit 2 weeks later. The primary endpoint was: • The change from Baseline to End of Treatment (Week 12) in mean "off" time in hours per day. The secondary 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. Tier 1 events were: • The incidences of SBP ≥180 mm Hg, DBP ≥105 mm Hg, ALT ≥3X ULN and ≥10% increase from Baseline, AST ≥3X ULN and ≥10% increase from Baseline, C-SSRS, Suicidality, and Epworth Sleepiness Scale score. [redacted] Sample case report forms are not required for a non-submission aCSR. [redacted]	
	Planned duration of main phase: Planned duration of screening phase:	12 weeks Up to 5 weeks
Objectives	The Primary Efficacy Objective of this trial was to evaluate the efficacy of the PRL doses, 2 mg BID and 5 mg BID, 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. The Key Secondary Efficacy Objectives for this trial were to evaluate the efficacy of the PRL doses 2 mg BID and 5 mg BID 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. The Primary Safety Objective of this trial was to assess the safety and tolerability of PRL compared with placebo in subjects with moderate to severe PD experiencing motor fluctuations and receiving a stable dose of L dopa.	
Hypotheses	Hypothesis 1: At least the 5 mg BID dose of PRL is superior to placebo as measured by the change from Baseline to Week 12 in the mean "off" time. Hypothesis 2: At least the 5 mg BID dose of PRL 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 5 mg BID dose of PRL is superior to placebo as measured by the change from Baseline to Week 12 in mean "on" time without troublesome dyskinesia.	
Treatments groups	PRL 2mg BID	PRL, 12 weeks, 2mg tablet, administered BID once in morning and again 8 hours later, 157 subjects
	PRL 5mg BID	PRL, 12 weeks 5mg tablet, administered BID once in morning and again 8 hours later, 157 subjects

	Placebo	Placebo, 12 weeks tablet, administered BID once in morning and again 8 hours later, 159 subjects

Clinical Supplies Table

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

[redacted]

Endpoints and definitions	Primary efficacy endpoint		The change from Baseline to End of Treatment (Week 12) in mean “off” time in hours per day.
	Secondary efficacy endpoint		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.
	Secondary efficacy endpoint		The change from Baseline to Week 12 in mean "on" time without troublesome dyskinesia in hours per day.
	Prespecified safety endpoints	Tier 1 events	The incidences of SBP ≥180 mm Hg, DBP ≥105 mm Hg, ALT ≥3X ULN and ≥10% increase from Baseline, AST ≥3X ULN and ≥10% increase from Baseline, C-SSRS, Suicidality, and Epworth Sleepiness Scale score.
Database lock	10-May-2013	Trial status	14-MAR-2011 first subject first visit to 16-APR-2013 last subject last visit
RESULTS AND ANALYSIS:	All analyses for efficacy and safety were performed according to the protocol [16.1.1]. Pharmacokinetic samples were analyzed for PRL according to the protocol [redacted]		
Analysis description	**Primary Efficacy Analysis**		
Analysis population and time point description	Full Analysis Set (FAS): All randomized subjects remaining after subjects were excluded for 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, lack of Baseline data for those analyses requiring Baseline data. All subjects as treated set (ASaT): All subjects who received at least one dose of study drug.		

Summary	Neither the PRL 2 mg BID nor the PRL5 mg BID treatment group demonstrated a statistically significant or clinically meaningful difference vs. placebo at the Week 12 time point for the primary endpoint. At the end of the study (Week 12), there was minimal separation observed among the treatment groups, with responses ranging from -0.8 hour decrease for placebo-treated subjects to -1.0 hours for PRL 2 mg BID and -1.1 hours for PRL 5 mg BID treatment groups.
Analysis description	**Key Secondary Efficacy Analysis**
Analysis population and time point description	FAS
Summary	Similarly, neither the PRL 2 mg BID nor the PRL 5 mg BID treatment group demonstrated a statistically significant and clinically meaningful difference vs. placebo at the Week 12 time point 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 drug.
Summary	Overall there was a higher percentage of AEs associated with the PRL treatment groups than with the placebo treatment groups.

A total of 476 subjects were randomized and of those 473 subjects were treated with study medication, 314 with PRL and 159 with placebo. A total of 423 subjects completed the trial: 139 subjects (88%) in the PRL 2mg BID group, 139 subjects (87%) in the PRL 5mg BID group, and 145 subjects (91%) placebo in the placebo group. [redacted]

A total of 6 (4%) subjects in the PRL 2 mg BID group, 10 (6%) subjects in the PRL 5 mg BID group, and 5 (3%) subjects in the placebo treatment group were discontinued due to an AE. There were 3 subjects discontinued from the trial because of an SAE, 1 (1%) subject in the 2 mg BID PRL treatment group, 1 (1%) subject in the 5 mg BID PRL treatment group, and 1 (3%) subject in the placebo treatment group. [redacted].

Subject Disposition - Treatment Phase (All Subjects Randomized)

Subject Disposition	PRL 2mg BID		PRL 5mg BID		All PRL		Placebo	
Randomized	158	(100)	159	(100)	317	(100)	159	(100)
Treated	157	(99)	157	(99)	314	(99)	159	(100)
FAS	154	(97)	153	(96)	307	(97)	158	(99)
Discontinued Treatment Phase	18	(11)	18	(11)	36	(11)	14	(9)
Adverse Event	6	(4)	10	(6)	16	(5)	5	(3)
Lost To Follow-Up	2	(1)	0		2	(1)	3	(2)
Subject Withdrew Consent	7	(4)	7	(4)	14	(4)	3	(2)
Non-Compliance With Protocol	2	(1)	1	(1)	3	(1)	0	
Did Not Meet Protocol Eligibility	0		0		0		1	(1)
Administrative	1	(1)	0		1	(<1)	2	(1)
Completed Treatment Phase	139	(88)	139	(87)	278	(88)	145	(91)

[redacted]

Overall, baseline demographics and disease characteristics were similar among the treatment groups. More male subjects were randomized in the trial; 62% to PRL treatment and 60% to placebo treatment. The mean ages of subjects were 62.9, 64.2, and 64.2 years for the PRL 2 mg BID, 5 mg BID, and placebo treatment groups respectively, with an overall age range of 33 to 84 years. The mean BMI was 26.5, 26.5, and 26.6 for the PRL 2 mg BID, 5 mg BID, and placebo treatment groups respectively, with an overall range of 14.5 to 51.4. The majority of subjects had a Hoehn and Yahr staging of 2.5 or 3 with ≤10% subjects in stage 4. The mean and median years of PD history was (8.50 and 7.85 years) and (8.17 and 7.00 years) for the all PRL and placebo treatment groups respectively, with an overall range of (1.0 to 25.3 years). The mean and median daily L Dopa dose was (726.2 mg and 625 mg) and (729.5 mg and 625 mg) for the all PRL and placebo treatment groups respectively, with an overall range of (125 to 3000 mg).

Summary of Demographics and Baseline Characteristics All Subjects as Treated

Baseline characteristics	PRL 2mg BID n=157	PRL 5mg BID n=157	All PRL n=314	Placebo n=159
Sex (n,%)				
Female	49 (31)	71 (45)	120 (38)	64 (40)
Male	108 (69)	86 (55)	194 (62)	95 (60)
Race (n,%)				
White	149 (95)	144 (92)	293 (93)	142 (89)

Summary of Demographics and Baseline Characteristics All Subjects as Treated

Baseline characteristics	PRL 2mg BID n=157	PRL 5mg BID n=157	All PRL n=314	Placebo n=159
Non-White	8 (5)	13 (8)	21 (7)	17 (11)
Ethnicity (n,%)				
Hispanic or Latino	40 (25)	40 (25)	80 (25)	43 (27)
Not Hispanic or Latino	117 (75)	117 (75)	234 (75)	116 (73)
Age (yrs)				
Mean (SD)	62.9 (9.0)	64.2 (8.7)	63.6 (8.9)	64.2 (8.9)
Median	63.0	64.0	64.0	64.0
Range	33 - 84	38 - 84	33 - 84	34 - 82
Age (n,%)				
30 - <55	29 (18)	23 (15)	52 (17)	23 (14)
55 - <65	62 (39)	57 (36)	119 (38)	61 (38)
65 - <75	49 (31)	61 (39)	110 (35)	59 (37)
>=75	17 (11)	16 (10)	33 (11)	16 (10)
Weight (kg)				
Mean (SD)	76.94 (16.56)	76.11 (17.41)	76.53 (16.97)	75.22 (17.62)
Median	75.30	76.20	75.78	72.79
Range	34.5 - 152.4	42.3 - 150.0	34.5 - 152.4	40.0 - 168.0
Missing	0	4	4	3
Height (cm)				
Mean (SD)	170.06 (10.09)	168.66 (10.80)	169.37 (10.45)	167.64 (10.19)
Median	170.18	170.00	170.00	167.00
Range	143.0 - 193.0	142.7 - 191.0	142.7 - 193.0	143.0 - 195.6
Missing	0	4	4	3
BMI				
Mean (SD)	26.50 (4.69)	26.52 (4.33)	26.51 (4.51)	26.64 (5.26)
Median	26.40	26.00	26.25	25.85
Range	14.5 - 45.6	16.6 - 41.3	14.5 - 45.6	15.2 - 51.4
Missing	0	4	4	3
Hoehn and Yahr Staging (n,%)				
Stage 2	0	0	0	2 (1)
Stage 2.5	89 (57)	76 (48)	165 (53)	79 (50)

Summary of Demographics and Baseline Characteristics All Subjects as Treated

Baseline characteristics	PRL 2mg BID n=157	PRL 5mg BID n=157	All PRL n=314	Placebo n=159
Stage 3	66 (42)	74 (47)	140 (45)	68 (43)
Stage 4	2 (1)	7 (4)	9 (3)	10 (6)
Caffeine Daily Use (n,%)				
None	46 (29)	54 (34)	100 (32)	51 (32)
>None - 1 cup/glass per day	61 (39)	52 (33)	113 (36)	64 (40)
>1 cups/glasses per day	50 (32)	51 (32)	101 (32)	44 (28)
PD History (Yrs)				
Mean (SD)	8.12 (4.58)	8.87 (4.59)	8.50 (4.59)	8.17 (4.78)
Median	7.20	8.20	7.85	7.00
Range	1.1 - 25.3	1.6 - 20.7	1.1 - 25.3	1.0 - 22.0
Total Daily L Dopa dose(mg)				
Mean (SD)	714.8 (401.0)	737.6 (388.4)	726.2 (394.3)	729.5 (423.2)
Median	600.0	625.0	625.0	625.0
Range	150.0 - 3300.0	100.0 - 2000.0	100.0 - 3300.0	125.0 - 3000.0
Missing	0	1	1	0

[redacted]

The summary of results in primary and key secondary endpoints and the change from Baseline "off" time is shown in the following table and figure:

Summary of Primary and Key Secondary Endpoints Full Analysis Set

Efficacy Parameter		Estimated Response		
		PRL 2mg BID N[a]=154	PRL 5mg BID N[a]=153	Placebo N[a]=158
Average OFF time	CFB (hours)	-1.0	-1.1	-0.8
	Diff vs PBO (hours) (95% CI)	-0.2 (-0.72, 0.35)	-0.3 (-0.86, 0.21)	
	p-value	0.493	0.236	
Percent Responders	Estimate (%)	37.1	36.9	30.5
	Diff vs PBO (%) (95% CI)	7.0 (-4.17, 18.05)	6.5 (-4.63, 17.61)	
	p-value[b]	0.244	0.262	
Average ON time without Troublesome Dyskinesia	CFB (hours)	0.6	0.7	0.5
	Diff vs PBO (hours) (95% CI)	0.1 (-0.47, 0.63)	0.1 (-0.44, 0.67)	
	p-value	0.776	0.683	

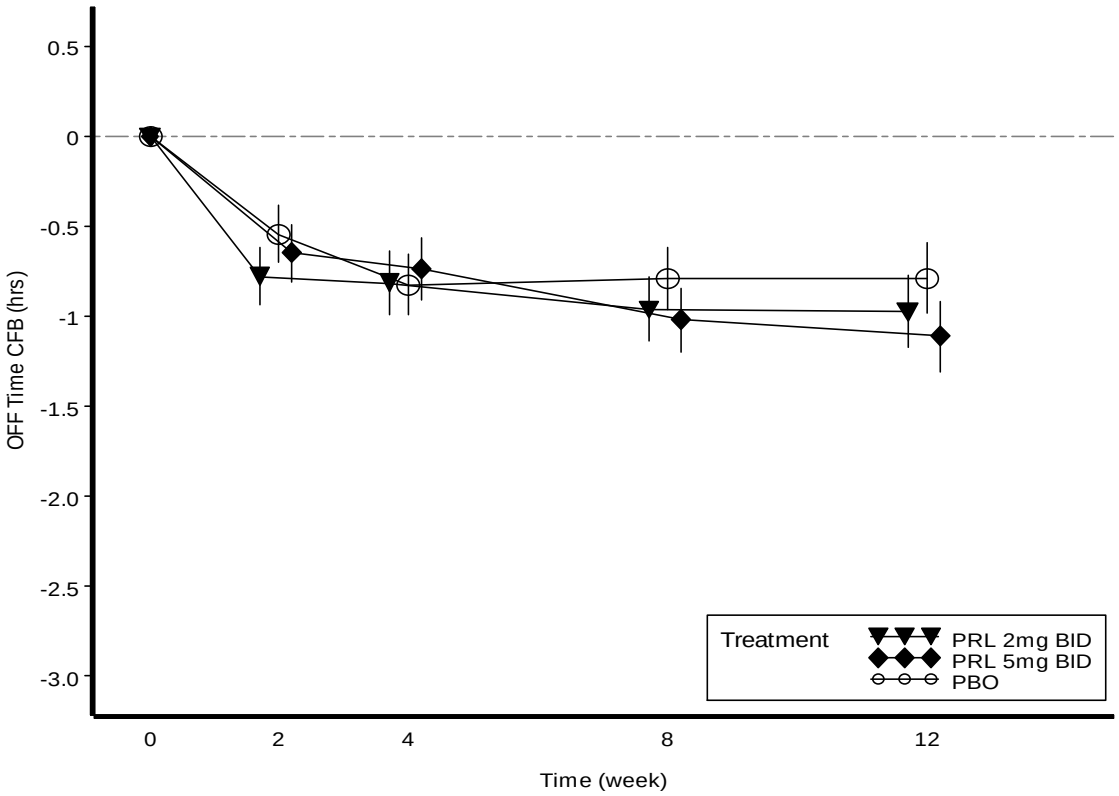
CFB = change from Baseline;

[a] N represents the number of randomized and treated subjects with at least one post-baseline value.

[b] p-value is for the estimated Odds Ratio based on a generalized linear mixed model with baseline average OFF time (hours/day) as a covariate and treatment-by-time interaction as fixed effect and patient as random effect.

[redacted]

P07037
Change from Baseline in Average OFF Time (hours) Over Time
Estimated Mean* +/- SE by Treatment Group
(Full Analysis Set)



* Estimated Mean and SE are derived from the primary statistical model

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 473 patients were treated. The AE percentages were higher in the PRL treated subjects than the placebo treated subjects. Of subjects treated, 94 (60%) of PRL 2 mg BID, 96 (61%) of PRL 5 mg BID, and 73 (46%) of placebo treated patients experienced at least 1 adverse event. The discontinuations due to drug related AEs were higher in the PRL treated subjects 6 (4%) and 9 (6%) for the PRL 2 mg BID and 5 mg BID, respectively, than in the placebo treated subjects 4 (3%). There were no marked differences in the amount of SAEs or drug related SAEs among the treatment groups. The overall amount of discontinuations due to serious drug related AEs was ≤ 1% for all treatment groups within the study. [redacted] The subject was a 62 year old male and in order to meet the eligibility criteria for the extension study, he had discussed switching antidepressants with his personal physician. Shortly after the switch, the subject shot himself and the incident was deemed possibly related to investigational product by the investigator. [redacted].

Clinical Adverse Experiences Summary All Subjects as Treated

	Number of Subjects (%)							
	PRL 2mg BID n=157		PRL 5mg BID n=157		All PRL n=314		Placebo n=159	
Number (%) of subjects with:								
One or more adverse events	94	(60)	96	(61)	190	(61)	73	(46)
Drug-related adverse events[a]	47	(30)	68	(43)	115	(37)	43	(27)
Serious adverse events[b]	5	(3)	2	(1)	7	(2)	4	(3)
Serious drug-related adverse events	2	(1)	0		2	(1)	2	(1)
Death	1	(1)	0		1	(<1)	0	
Discontinuation due to adverse event	6	(4)	10	(6)	16	(5)	4	(3)
Discontinuation due to drug-related adverse event	6	(4)	9	(6)	15	(5)	3	(2)
Discontinuation due to serious adverse event	1	(1)	1	(1)	2	(1)	1	(1)
Discontinuation due to serious drug-related adverse event	1	(1)	0		1	(<1)	1	(1)

[a] Determined by the investigator to be possibly, probably, or definitely drug-related

[b] All serious adverse events are reported, regardless of treatment emergence

[c] Every subject is counted a single time for each applicable specific adverse event

[redacted]

Constipation, nausea, and dyskinesia were reported more frequently in the PRL 5 mg BID group compared to PRL 2mg BID and placebo treatment groups.

No subjects reported ALT or AST elevations greater than 3x upper limit of normal.

Changes from Baseline in supine SBP and DBP were higher in the PRL treated groups than in subjects treated with placebo. This difference was noted on Day 1 after the first dose of study drug and lessened during the trial. The Day 1 increases of ~2 mmHg to 4 mmHg in PRL-treated subjects returned to baseline levels from Week 2 onward, while the mean decrease from baseline of ~2 mmHg observed in placebo-treated subjects was similar at all post-treatment timepoints. It is notable that the baseline values in supine SBP were 120 mmHg in the PRL groups compared to 123 mmHg in the placebo group and that some of the magnitude of the change from baseline differences may be due to a regression to the mean.

A similar overall trend was noted in supine DBP where the baseline mean values also differed slightly between PRL and placebo treatment groups. The Baseline values in supine DBP were 74 mmHg in the PRL treated groups compared to 76 mmHg in the placebo group.

The changes from baseline in total ESS at week 12 in the PRL 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 PRL placebo treatment groups. The summary of sleep attack questionnaire showed similar incidences of sleep attack between all treatment groups.

CONCLUSIONS:

- This study with placebo control is a negative study. Neither the PRL 2 mg or 5 mg BID treatment group demonstrated a statistically significant and clinically meaningful difference vs. placebo at the Week 12 time point in the primary and key secondary efficacy endpoints.
- PRL was generally well tolerated in this trial.
- 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 (≤ 6%) 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 no ALT or AST elevations ≥ 3 x ULN and ≥ 10% increase from baseline. 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. There were no clinically relevant changes in other laboratory values.
- Overall the changes in BP for the preladenant treatment groups were small and similar to the placebo treatment group.
- Incidences of insomnia, changes from baseline in ESS, and incidences of sleep attack were similar and small among all treatment groups.

PUBLICATIONS: None