SYNOPSIS

Name of Sponsor:
Solvay Pharmaceuticals

Individual Study Table:

(For National Authority Use only)

Name of Finished Product:
Pardoprunox

Name of Active Ingredient:
Pardoprunox (SLV308)

Study Title:
The Vermeer Study:
A Multicenter, Randomized, Double Blind, Parallel-group Placebo and Pramipexole Controlled Study to Assess Efficacy and Safety of SLV308 Monotherapy in the Treatment of Patients with Early Stage Parkinson's Disease.

Investigator(s):
78 Principal Investigators.

Study Center(s):
78 centers in 17 countries.

Publication (Reference):
Not applicable.

Study Period:

10 NOV 2006 (first subject first visit) to
13 FEB 2008 (last subject last visit)

Phase of Development:
III

Objectives:
The primary objective of this study was to provide six months pivotal efficacy data by showing that 12-42 mg/day pardoprunox (SLV308) monotherapy is superior to placebo with respect to the effect on motor functioning of Parkinson's disease (PD) subjects.

The secondary objectives were:

- To investigate the effects of treatment with pardoprunox compared to placebo in improving overall PD symptoms, including activities of daily living (ADL) and Clinical Global Impression (CGI).
- To collect and evaluate data on population-pharmacokinetics of pardoprunox.
- To investigate the effects of pardoprunox treatment on health-related quality of life.
- To compare pramipexole treatment with placebo for testing assay sensitivity and for exploratory purposes only.

The safety objective was to assess the safety and tolerability of pardoprunox monotherapy in subjects with early stage PD.

Methodology:
This multicenter trial was a randomized, double blind, parallel group study of six months maintenance treatment with pardoprunox as monotherapy in subjects with early stage PD. Approximately 330 subjects were intended to be randomized to three possible treatment groups

(110 subjects per group): one pardoprunox treatment group (maintenance doses of 12-42 mg/day), one pramipexole treatment group (maintenance doses of 1.5-4.5 mg/day) and one placebo treatment group. The study was planned for about 100 centers in approximately 20 countries. The study consisted of a one-week screening period, a four to seven-week fixed-flexible titration period, a 24-week maintenance period and a one-week follow-up for subjects not continuing in the open label safety extension study.

Subjects meeting all of the inclusion criteria and none of the exclusion criteria were randomized to one of the three treatment groups at the end of the screening period (baseline). All subjects were titrated over a period of three weeks to dose level 1 corresponding with doses of 12 mg/day for the pardoprunox group and 1.5 mg/day for the pramipexole treatment group. For Weeks 4-7, individual dose adjustments were performed to find the optimal dose for the maintenance period in terms of tolerability and efficacy. For the pardoprunox treatment group this was in the defined range of 12-42 mg/day (dose levels 1-5: 12, 18, 24, 30 or 42 mg/day, respectively) and for the pramipexole group this was in the range of 1.5-4.5 mg/day (dose levels 1-5: 1.5, 2.25, 3.0, 3.75 or 4.5 mg/day, respectively). The dose titration was to continue up to the optimum individual dose as judged by the investigator on the basis of tolerability (e.g., nature and severity of adverse events [AEs] did not support further dose escalation) and efficacy (e.g., if there was no further clinical improvement the dose escalation was stopped). If subjects experienced intolerability during the individual dose adjustment period which limited further titration they were instructed by the investigator to decrease the total daily dose to the dose level of the visit before and this dose level was kept for the entire maintenance period. However, these dose reductions were only performed if subjects were in the fourth week of titration (doses above 12 mg/day in the pardoprunox group and above 1.5 mg/day in the pramipexole group). In the event of treatment emerging psychiatric symptoms such as psychosis, hallucinations, illusions, confusion, vivid dreams, the dose of study medication had to be reduced by one level (for subjects on dose level 2 or higher) until the AE resolved or the patient was withdrawn from the study. If treatment with study drug was terminated, the appropriate dose tapering was followed. For the placebo group, dummy steps were taken in order to maintain the blind.

The maintenance period lasted for 24 weeks. There were five defined possible maintenance dose levels (for pardoprunox corresponding with 12, 18, 24, 30 or 42 mg/day and for pramipexole corresponding with 1.5, 2.25, 3.0, 3.75 or 4.5 mg/day). During the maintenance period the dose of study medication was, in principle, to be kept stable. However, the dose of study medication might be reduced by one level (for subjects on dose level 2 or higher) if a medical reason (e.g., an AE) required dose reduction for resolution. If one dose reduction was not sufficient, the subject was to terminate the study prematurely. In the event of treatment emerging psychiatric symptoms such as psychosis, hallucinations, illusions, confusion, vivid dreams, the dose of study medication had to be reduced by one level (for subjects on dose level 2 or higher) until the AE resolved or the patient was withdrawn from the study. If treatment with study drug was terminated, the appropriate dose tapering was followed. The last visit for this study was the first visit for the double-blind titration period of the six-month open label safety extension study, described in a separate protocol (S308.3.008). Subjects who did not sign the informed consent and subjects who were not eligible for enrollment into the open label safety extension underwent a one-week follow-up for withdrawal of study medication, during which adding anti-Parkinson medication was avoided, if the subject's condition allowed. For these subjects and those who prematurely discontinued the current study, pardoprunox and pramipexole treatment was tapered

(if needed based on the dose level reached) and withdrawn during this one-week period and safety date was collected.

Number of Subjects (Planned, Consented, Randomized and Analyzed):
Planned: 330 subjects (110 subjects to 12-42 mg/day pardoprunox, 110 subjects to 1.5-4.5 mg/day pramipexole and 110 subjects to placebo).

Consented: 385 subjects.

Randomized: 334 subjects (108 subjects to 12-42 mg/day pardoprunox, 116 subjects to 1.5-4.5 mg/day pramipexole and 110 subjects to placebo).

Analyzed safety: 334 subjects (108 subjects to 12-42 mg/day pardoprunox, 116 subjects to 1.5-4.5 mg/day pramipexole and 110 subjects to placebo).

Analyzed Full Analysis Sample (FAS): 329 subjects (104 subjects to 12-42 mg/day pardoprunox, 115 subjects to 1.5-4.5 mg/day pramipexole and 110 subjects to placebo).

Analyzed Per-protocol (PP): 288 subjects (84 subjects to 12-42 mg/day pardoprunox, 105 subjects to 1.5-4.5 mg/day pramipexole and 99 subjects to placebo).

Diagnosis and Main Criteria for Inclusion:
Male or female subjects ≥ 30 years old with early stage PD and modified Hoehn and Yahr up to stage 3 and a Unified Parkinson's Disease Rating Scale (UPDRS) motor score (part 3) with a total of at least 10 at baseline.

Test Product, Dose and Mode of Administration, Batch Number:
Pardoprunox oral gelatin capsules: total daily dose 0.3 mg to 42 mg (three times daily [tid] regimen). Subjects were titrated from 0.3 to 12 mg/day over a period of three weeks. For Weeks 4-7, subjects were titrated to their optimal dose within the range of 12-42 mg/day. During a 24-week maintenance period, there were five possible maintenance dose levels (12, 18, 24, 30 or 42 mg/day).

Batch numbers: 69658, 69659, 69664, 69688, 69954, 69959, 69997, 69998, 70105, 70106, 70107, 70111, 70251, 70252, 70254, 70255, 70258, 70316, 70317, 70506.

Duration of Treatment:
Up to 31 weeks.

Reference Therapy, Dose and Mode of Administration, Batch Number:
Pramipexole oral gelatin capsules (matching pardoprunox): total daily dose 0.375 mg to 4.5 mg (tid regimen). Subjects were titrated from 0.375 to 1.5 mg/day over a period of three weeks. For Weeks 4-7, subjects were titrated to their optimal dose within the range of 1.5 to 4.5 mg/day. During a 24-week maintenance period, there were five possible maintenance dose levels (1.5, 2.25, 3.0, 3.75 and 4.5 mg/day).

Batch number: 70145, 70147, 70148, 70149, 70150, 70151, 70152, 70153, 70154, 70424, 70426, 70449, 70450, 70703, 70705, 70710, 70711.

Placebo capsules matching pardoprunox, taken orally (tid).

Batch number: 70023, 70488.

Criteria for Evaluation

Efficacy:
Primary efficacy variable: change from baseline to endpoint in the total UPDRS motor score (part 3).

Key secondary variables: change from baseline to endpoint in the UPDRS ADL (UPDRS, part 2) score, CGI-Improvement (CGI-I) score, change from baseline to endpoint in the Parkinson's Disease Questionnaire (PDQ-39) total score.

Safety:
Adverse events, vital signs, physical examination, electrocardiogram (ECG), laboratory assessments and Epworth Sleepiness Scale (ESS).

Statistical Methods:
Efficacy:

The primary efficacy variable was the change from baseline to endpoint in the total UPDRS motor score (part 3). Analysis of covariance (ANCOVA) models with fixed factors treatment group (pardoprunox, pramipexole or placebo) and country, and the baseline value as covariate were employed. The pair-wise comparison of pardoprunox versus placebo was done in the ANCOVA model as contrast. The comparison of pramipexole versus placebo was conducted as descriptive analyses to assess the assay sensitivity. In order to explore the impact of missing data, sensitivity analyses were conducted, i.e., a mixed-effect model and an ANCOVA model with the missing pattern as extra stratification factor included. The treatment by country interaction was examined in a separate analysis that had an additional treatment by country interaction term in the model.

Key secondary parameters were defined in order of their importance: the change from baseline of the UPDRS part 2 score, the CGI-I score and the change from baseline of the PDQ-39 total score at Week 24 maintenance visit. A hierarchical testing procedure was applied using the above mentioned order of the parameters only based on the comparison between the pardoprunox and the placebo group. Each of the tests was applied at the 5% level of significance. A similar ANCOVA as that used for analyzing the primary efficacy variable was applied to the changes from baseline of the UPDRS part 2 score and the PDQ-39 total score. A non-parametric van Elteren's test stratified by country was performed in the analysis of CGI-I score at Week 24 maintenance/endpoint. This test was applied for each of the two comparisons of pardoprunox and pramipexole dose group versus placebo. However, only the results of the comparison between pardoprunox and placebo were used in the hierarchical test procedure of the key secondary parameters. The comparison of pramipexole versus placebo was conducted as descriptive analyses to assess the assay sensitivity. The pramipexole treatment group was compared with the pardoprunox treatment group by means of descriptive statistics of the primary and key secondary outcome parameters.

Other secondary parameters were summarized and compared using appropriate statistical methods. The other secondary efficacy variables included the changes from baseline of the UPDRS part 1, parts 2+3, parts 1+2+3 and the scores on the eight sub-scales of the PDQ-39, the CGI-Severity, the responder rate, absolute values and changes from baseline in Schwab and England ADL score and the changes from baseline of the EQ-5D score. In particular, the responder (i.e., $\geq$ 20% decrease from baseline in UPDRS motor score) rates were compared between the pardoprunox and the placebo group using the Cochran-Mantel-Haenszel test with country as strata.

Safety:

All safety parameters were presented by descriptive statistics for each treatment separately. For each unique treatment, treatment emergent adverse events (TEAEs) were summarized per

primary system organ class (SOC), per high level term (HLT) by primary SOC and per preferred term (PT) by HLT and primary SOC. Severity and drug-event relationship of TEAEs were summarized separately. The occurrence of selected AEs was presented by time-interval. Values of laboratory variables, vital signs, 12-lead ECGs and ESS scores, including changes from baseline, were summarized. A frequency table and subject listings were presented for markedly abnormal values. Shift tables were presented according to the reference ranges (low, normal or high). Concomitant medication, including coding data, were summarized per assigned treatment period for incidence per subject, for primary therapeutic subgroup and for generic name by therapeutic subgroup. In addition, prior medications were presented.

Summary – Conclusions

A total of 334 subjects were randomized, of whom, 108 subjects prematurely withdrew from the study. The following table summarizes subject disposition.

Subject disposition (all randomized subjects)

	SLV308 12-42 mg/day N=108	**Pramipexole 1.5-4.5 mg/day N=116**	**Placebo N=110**
Overall			
No. (%) of subjects who completed the study	52 (48.1%)	86 (74.1%)	88 (80.0%)
No. (%) of subjects who terminated the study	56 (51.9%)	30 (25.9%)	22 (20.0%)
Primary reason for premature study termination			
Adverse event	50 (46.3%)	16 (13.8%)	7 (6.4%)
Lack of efficacy	0	3 (2.6%)	11 (10.0%)
Lost to follow-up	1 (0.9%)	1 (0.9%)	0
Withdrew consent	5 (4.6%)	5 (4.3%)	3 (2.7%)
Protocol violation	0	5 (4.3%)	1 (0.9%)

All 334 randomized subjects were included in the safety sample, of whom 329 were included in the FAS. The following table summarizes analysis samples (safety and FAS).

Analysis samples (all randomized subjects)

	SLV308 12-42 mg/day N=108	**Pramipexole 1.5-4.5 mg/day N=116**	**Placebo N=110**
No. (%) of subjects in the safety sample	108 (100.0%)	116 (100.0%)	110 (100.0%)
No. (%) of subjects excluded from the safety sample	0	0	0
No. (%) of subjects in the FAS	104 (96.3%)	115 (99.1%)	110 (100.0%)
No. (%) of subjects excluded from the FAS	4 (3.7%)	1 (0.9%)	0
No post-baseline efficacy evaluation	2 (1.9%)	0	0
Only one post-baseline UPDRS assessment which occurred > 7 days after end of treatment	2 (1.9%)	1 (0.9%)	0

The following table summarizes subject demographics.

Demographics (FAS)

		SLV308 12-42 mg/day N=104	Pramipexole 1.5-4.5 mg/day N=115	Placebo N=110
Age (yrs)	N	104	115	110
	Mean (range)	62.9 (38-83)	60.8 (30-88)	62.8 (40-81)
Gender	Male, n (%)	55 (52.9%)	62 (53.9%)	69 (62.7%)
	Female, n (%)	49 (47.1%)	53 (46.1%)	41 (37.3%)
Race	Asian, n (%)	31 (29.8%)	32 (27.8%)	30 (27.3%)
	Black, of African heritage or African American	3 (2.9%)	0	2 (1.8%)
	White	70 (67.3%)	83 (72.2%)	78 (70.9%)

Efficacy Results:

The following table summarizes the statistical analysis of the change from baseline to endpoint in the primary efficacy variable (total UPDRS motor score, part 3).

UPDRS, part 3 – LOCF (FAS)

Time point		SLV308 12-42 mg/day N=104	Pramipexole 1.5-4.5 mg/day N=115	Placebo N=110
Baseline	N	104	115	110
	Mean (SD)	22.2 (9.07)	23.2 (9.08)	20.6 (7.83)
Change from baseline to endpoint	N	104	115	110
	Mean (SD)	-5.3 (6.55)	-6.2 (8.18)	-2.5 (8.56)
	Adjusted mean (SE)	-4.9 (0.69)	-5.7 (0.66)	-2.5 (0.68)
	Difference to placebo			-
	Estimate	-2.4	-3.1	
	(95% CI)	(-4.2, -0.6)	(-5.0, -1.1)	
	p-value versus placebo	0.0091	0.0020	-

In the FAS using the last observation carried forward (LOCF) approach, at the end of the titration period and the overall endpoint, all groups showed a reduction in UPDRS, part 3 from baseline and a statistically significant difference was observed between both the pardoprunox and pramipexole groups and placebo. Statistically significant reductions from baseline in UPDRS, part 3 were observed in the pardoprunox group from titration Week 2 until the endpoint and in the pramipexole group from titration Week 4 until endpoint. There was no indication of a treatment-by-country interaction in the change from baseline in the UPDRS, part 3 to endpoint. In addition to the LOCF approach, statistical analysis was performed to include subjects who completed 24 weeks of maintenance treatment (observed cases [OC]). Results were similar to the LOCF analyses.

Results with the FAS were consistent with analysis of the PP sample.

In order to explore the impact of missing data, sensitivity analyses were performed. Two approaches were used. The first approach was to apply a mixed effects model to the OC data and the second approach was to apply a pattern mixture model. For the latter approach, data was grouped according to when subjects had their last analyzable UPDRS, part 3 assessment. The results of the mixed effects analyses and missing pattern analyses supported the LOCF analysis.

The following table summarizes the statistical analysis of the changes from baseline to endpoint for the key secondary efficacy variables (UPDRS part 2 score and PDQ-39 total score) as well as the CGI-improvement at endpoint.

UPDRS (part 2), CGI-Improvement score, PDQ-39 total score – LOCF (FAS)

Change from baseline to endpoint		**SLV308 12-42 mg/day N=104**	**Pramipexole 1.5-4.5 mg/day N=115**	**Placebo N=110**
UPDRS, part 2	Mean (SD)	-1.31 (3.44)	-1.58 (3.72)	-0.46 (3.28)
	Difference to placebo Estimate (95% CI)	-0.8 (-1.6, -0.1)	-0.9 (-1.8, -0.1)	-
	p-value versus placebo	0.0715	0.0360	-
CGI-Improvement	Very much improved	3 (2.9%)	7 (6.1%)	1 (0.9%)
	Much improved	27 (26.5%)	35 (30.4%)	24 (22.2%)
	p-value versus placebo	0.053	0.008	-
PDQ-39 total score	Mean (SD)	1.02 (9.68)	-1.12 (10.05)	0.28 (8.17)
	Difference to placebo Estimate (95% CI)	0.9 (-1.5, 3.2)	-1.0 (-3.3, 1.3)	-
	p-value versus placebo	0.4664	0.3970	-

For the key secondary efficacy variables; at endpoint all groups showed a reduction in UPDRS, part 2 with a statistically significant difference observed between the pramipexole and placebo group. The proportion of subjects with a CGI-I score of 'very much improved' or 'much improved' was higher in the pramipexole group compared with the pardoprunox and placebo groups. A statistically significant difference in the CGI-Improvement score was observed between the pramipexole group and the placebo group at endpoint. The change from baseline in PDQ-39 total score to endpoint for the pardoprunox and pramipexole groups compared to placebo was not statistically significant. For the other secondary efficacy variables; pardoprunox demonstrated similar efficacy to pramipexole from baseline to endpoint, except in UPDRS, part 1 (a small increase from baseline to endpoint was observed with pardoprunox compared to a small decrease from baseline in the pramipexole group; no statistically significant differences were observed between the active groups and placebo) and UPDRS, part 3 responders (while both the pardoprunox and pramipexole groups had higher proportions of responders than placebo, the difference was only statistically significantly for the pramipexole group). Similar efficacy results were observed for the OC analyses for all other secondary variables except for some small differences in the bodily discomfort subscore for PDQ-39.

No significant interaction on the primary efficacy parameter was observed between treatment and age, gender, baseline use of anti-PD medication, MAO-B inhibitor use or smoking status.

Safety Results:

A total of 344 subjects were included in the safety sample. Two hundred and seventy four subjects were reported with at least one TEAE during the study (100 [92.6%] subjects in the pardoprunox group, 97 [83.6%] subjects in the pramipexole group and 77 [70.0%] subjects in the placebo group).

No subjects died during the study. Twenty two subjects were reported with at least one TESAE, with a higher proportion observed in the pardoprunox group (12 [11.1%] subjects) compared to the other groups (seven [6.0%] subjects in the pramipexole group and three [2.7%] subjects in the placebo group). No TESAE was reported in more than one subject in any treatment group.

Seventy five subjects prematurely withdrew from the study due to a TEAE. The proportion of subjects reported to have prematurely withdrawn from the study due to a TEAE was higher in the pardoprunox group (50 [46.3%] subjects) compared with the pramipexole group (17 [14.7%] subjects) and the placebo group (eight [7.3%] subjects).

The majority of TEAEs were mild to moderate in severity. The highest proportion of subjects with severe TEAEs was reported in the pardoprunox group (26 [24.1%] subjects) compared with the other groups (13 [11.2%] subjects in the pramipexole group and four [3.6%] subjects in the placebo group). The most commonly reported severe TEAEs, reported by ≥ 3 subjects in the pardoprunox group, were nausea (six [5.6%] subjects in the pardoprunox group, two [1.7%] subjects in the pramipexole group and one [0.9%] subject in the placebo group), somnolence (five [4.6%] of subjects in the pardoprunox group and no subjects in the pramipexole and placebo groups), visual hallucinations (three [2.8%] subjects in the pardoprunox group, one [0.9%] subjects in the pramipexole group and no subjects in the placebo group) and confusional state (three [2.8%] subjects in the pardoprunox group and no subjects in the pramipexole and placebo groups).

The most common TEAEs, reported by ≥ 5% of subjects in any treatment group, by PT, are summarized by SOC and PT in the following table.

Incidence of TEAEs in ≥ 5% by PT of the subjects in any treatment group (safety sample)

Primary SOC PT	Sta- tistic	SLV308 12-42 mg/day (N =108)	Pramipexole 1.5-4.5 mg/day (N =116)	Placebo (N =110)
GASTROINTESTINAL DISORDERS				
ABDOMINAL PAIN UPPER	n (%)	5 (4.6%)	6 (5.2%)	4 (3.6%)
CONSTIPATION	n (%)	9 (8.3%)	12 (10.3%)	5 (4.5%)
DIARRHOEA	n (%)	5 (4.6%)	6 (5.2%)	3 (2.7%)
DYSPEPSIA	n (%)	4 (3.7%)	7 (6.0%)	4 (3.6%)
NAUSEA	n (%)	49 (45.4%)	38 (32.8%)	9 (8.2%)
VOMITING	n (%)	12 (11.1%)	3 (2.6%)	3 (2.7%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
ASTHENIA	n (%)	7 (6.5%)	2 (1.7%)	1 (0.9%)
FATIGUE	n (%)	7 (6.5%)	6 (5.2%)	6 (5.5%)
OEDEMA PERIPHERAL	n (%)	3 (2.8%)	14 (12.1%)	6 (5.5%)
INFECTIONS AND INFESTATIONS				
UPPER RESPIRATORY TRACT INFECTION	n (%)	6 (5.6%)	5 (4.3%)	3 (2.7%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS				
ARTHRALGIA	n (%)	0	6 (5.2%)	4 (3.6%)
BACK PAIN	n (%)	7 (6.5%)	4 (3.4%)	6 (5.5%)
NERVOUS SYSTEM DISORDERS				
DIZZINESS	n (%)	36 (33.3%)	21 (18.1%)	11 (10.0%)
HEADACHE	n (%)	12 (11.1%)	10 (8.6%)	11 (10.0%)
PARAESTHESIA	n (%)	11 (10.2%)	2 (1.7%)	2 (1.8%)
SOMNOLENCE	n (%)	45 (41.7%)	28 (24.1%)	8 (7.3%)
PSYCHIATRIC DISORDERS				
ANXIETY	n (%)	6 (5.6%)	3 (2.6%)	2 (1.8%)
HALLUCINATION, VISUAL	n (%)	19 (17.6%)	5 (4.3%)	1 (0.9%)
INSOMNIA	n (%)	18 (16.7%)	10 (8.6%)	3 (2.7%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
HYPERHIDROSIS	n (%)	7 (6.5%)	1 (0.9%)	4 (3.6%)

Note Cut point (5%) is applied to incidence of PT.

The most commonly reported TEAEs were nausea and somnolence, both of which were reported at the highest incidence in the pardoprunox group.

The proportion of subjects with at least one related TEAE was also higher in the pardoprunox group (90 [83.3%] subjects) compared with the other groups (78 [67.2%] subjects in the pramipexole group and 45 [40.9%] subjects in the placebo group).

The most commonly reported TEAEs by SOC were nervous system disorders (71 [65.7%] subjects in the pardoprunox group, 55 [47.4%] subjects in the pramipexole group and 32 [29.1%] subjects in the placebo group), gastrointestinal disorders (62 [57.4%] subjects, 56 [48.3%]

subjects and 29 [26.4%] subjects, respectively) and psychiatric disorders (46 [42.6%] subjects, 29 [25.0%] subjects and 19 [17.3%] subjects, respectively).

The most commonly reported treatment related nervous system disorders by PT were somnolence (43 [39.8%] subjects in the pardoprunox group, 26 [22.4%] subjects in the pramipexole group and seven [6.4%] subjects in the placebo group) and dizziness (32 [29.6%], 16 [13.8%] and seven [6.4%] subjects, respectively). The most commonly reported treatment related gastrointestinal disorders were nausea (48 [44.4%] subjects in the pardoprunox group, 34 [29.3%] subjects in the pramipexole group and four [3.6%] subjects in the placebo group) and vomiting (12 [11.1%] subjects in the pardoprunox group, two [1.7%] subjects in the pramipexole group and two [1.8%] subjects in the placebo group). The most commonly reported treatment related psychiatric disorders were the perception disturbances, namely visual hallucinations (19 [17.6%], five [4.3%] and one [0.9%] subjects in the pardoprunox, pramipexole and placebo groups, respectively). Insomnia was reported for 14 (13.0%) subjects in the pardoprunox group, eight (6.9%) subjects in the pramipexole group and two (1.8%) subjects in the placebo group. All of these TEAEs were reported in higher proportions of subjects in the pardoprunox group and the vast majority of events started during the titration period with very few new events observed for the maintenance period.

The most commonly reported events of special interest were headache (12 [11.1%] subjects in the pardoprunox group, 10 [8.6%] subjects in the pramipexole group and 11 [10.0%] subjects in the placebo group), constipation (nine [8.3%], 12 [10.3%] and five [4.5%] subjects, respectively), diarrhea (five [4.6%], six [5.2%] and three [2.7%] subjects, respectively) and anxiety (six [5.6%], three [2.6%] and two [1.8%] subjects, respectively). Three (2.8%) subjects in the pardoprunox group, four (3.4%) subjects in the pramipexole group and three (2.7%) subjects in the placebo group were reported with a TEAE of hypertension.

The numbers of subjects with at least one TEAE leading to the use of concomitant medication were 61 (56.5%) subjects in the pardoprunox group, 53 (45.7%) subjects in the pramipexole group and 48 (43.6%) subjects in the placebo group. The most commonly reported TEAEs leading to the use of concomitant medication for the pardoprunox group were nausea (17 [15.7%] subjects), and back pain, constipation, insomnia and vomiting (each four [3.7%] subjects). The numbers of subjects with at least one TEAE leading to a dose reduction of study drug was greater in the pardoprunox group (36 [33.3%]) compared to 14 (12.1%) subjects in the pramipexole group and eight (7.3%) subjects in the placebo group. The most commonly reported TEAEs leading to a dose reduction of pardoprunox were dizziness, nausea and somnolence.

When presented by age, there was no apparent difference in the incidence of TEAEs. A slightly greater proportion of subjects ≥ 65 years of age had at least one TESAE in the pardoprunox group compared to subjects < 65 years of age and a slightly greater proportion of subjects ≥ 65 years of age had at least one severe TEAE in the pardoprunox group compared to subjects < 65 years of age.

When presented by gender, there was no apparent difference in the incidence of TEAEs. A slightly greater proportion of male subjects had at least one TESAE in the pardoprunox group compared to female subjects: eight (14.0%) compared to four (7.8%) subjects, respectively, and a slightly greater proportion of male subjects had at least one severe TEAE in the pramipexole group compared to female subjects: nine (14.3%) compared to four (7.5%) subjects, respectively.

Approximately half of the TEAEs were resolved by the end of the study (48.1% of subjects in the pardoprunox group, 49.1% of subjects in the pramipexole group and 57.3% of subjects in the placebo group). The most common TEAEs continuing or with missing outcome beyond the end of the study treatment were somnolence (21 [19.4%] subjects in the pardoprunox group, 14 [12.1%] subjects in the pramipexole group and four [3.6%] subjects in the placebo group) and dizziness (13 [12.0%] subjects in the pardoprunox group, nine [7.8%] subjects in pramipexole group and five [4.5%] subjects in the placebo group).

The numbers of subjects with at least one post-treatment AE (defined as those AEs starting more than seven days after the last intake of study medication during the titration/maintenance phase) were low across the three groups.

No clinically relevant changes from baseline in any quantitative laboratory parameter or qualitative urinalysis parameters were observed during the study, except in total CPK which showed median increases from baseline to endpoint in all treatment groups (18.5 IU/L in the pardoprunox group, 17.0 IU/L in the pramipexole group and 6 IU/L in the placebo group). Abnormally high CPK was reported in a total of 10 subjects (six [6.3%] subjects in the pardoprunox group, three [2.7%] subjects in the pramipexole group and one [0.9%] subject in the placebo group). Increased blood CPK considered by the investigator as clinically relevant and therefore a TEAE was reported in two subjects (one [0.9%] subject in each of the pardoprunox and pramipexole groups). Abnormally high CPK-MB levels were reported in five of the 10 subjects with abnormally high CPK, three subjects in the pardoprunox group and two subjects in the pramipexole group; however, none of these values were considered to be clinically relevant to be reported as a TEAE.

Changes from baseline to endpoint in vital sign parameters were similar across all groups. There were no notable changes from baseline to endpoint in any of the vital sign parameters, except more subjects had decreased weight in the pardoprunox group than in the pramipexole or placebo groups. During the study, the incidence of marked abnormalities in vital signs was similar across all groups, except in standing DBP and weight. Five (4.3%) subjects in the pramipexole group were reported with a standing DBP of $\geq$ 105 mmHg and an increase of $\geq$ 15 mmHg compared to no subjects in the other groups, and a higher proportion of subjects in the pardoprunox group was reported with a decrease in weight of $\geq$ 7% compared to the other groups (15 [14.6%] subjects in the pardoprunox group, 10 [8.8%] subjects in the pramipexole group and five [4.5%] subjects in the placebo group). One (0.9%) subject in the pramipexole group had a change from baseline of > 60 msec (mean of triplicate measurements) in QTcB and QTcF compared to no subjects in the other groups. One (1.0%), three (2.7%) and two (1.9%) subjects in the pardoprunox, pramipexole and placebo groups, respectively, had a maximum QTcB measurement of > 480 msec. One subject in both the pardoprunox (1.0%) and pramipexole (0.9%) groups had a maximum QTcB value of > 500 msec and no subjects had a maximum QTcF measurement of > 500 msec during the study.

Five subjects (three [2.8%] in the pardoprunox group, one [0.9%] in the pramipexole group and one [0.9%] in the placebo group) were reported with a TEAE of syncope; 3 subjects (one [0.9%], none and two [1.8%] subjects, respectively) had QTc interval prolongation on the ECG which was judged by the investigator to be clinically relevant and was reported as a TEAE of ECG QTc interval prolongation; and one (0.9%) subject in the placebo group was reported with a TEAE of ventricular tachycardia.

Conclusions:

- Pardoprunox showed a statistically significant better efficacy than placebo with respect to the primary efficacy parameter, UPDRS motor score.
- The primary efficacy outcome was supported by secondary parameters.
- Pramipexole showed a statistically significant better efficacy than placebo with respect to UPDRS motor score, in the same range as pardoprunox.
- Pardoprunox compared to pramipexole and placebo groups showed a higher incidence of AEs, an increased number of dose reductions due to AEs and more AEs leading to study termination indicating that the current titration was too rapid and selected dose range too high in early stage PD.