SYNOPSIS

Name of Sponsor:
Solvay Pharmaceuticals

Individual Study Table:

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Name of Finished Product:
Pardoprunox

Name of Active Ingredient:
Pardoprunox (SLV308)

Study Title:
An extension of the Vermeer study: An open-label SLV308 safety extension to study S308.3.003 in early PD patients

Investigator(s):
56 Investigators.

Study Center(s):
56 centers in 15 countries.

Publication (Reference):
Not applicable.

Study Period:
26 JUN 2007 (first subject first visit) to
12 SEP 2008 (last subject last visit)

Phase of Development:
III

Objectives:
The primary objective of this study was to collect and evaluate long-term safety and tolerability data of pardoprunox (SLV308) treatment in early Parkinson's disease (PD) patients.

The secondary objectives were:

- To collect descriptive efficacy data with respect to the motor functioning of PD patients and overall PD symptoms, including activities of daily living (ADL) and global clinical impression (CGI), after long-term treatment with pardoprunox in the dose range of 6-42 mg/day.
- To investigate the effects of long-term pardoprunox treatment on health-related quality of life.
- To collect and evaluate date on population-pharmacokinetics of pardoprunox.

Methodology:
This was a multicenter, six month open-label safety extension study for all subjects who were willing and eligible to continue treatment with pardoprunox after completion of the pivotal, double blind S308.3.003 trial (in the S308.3.003 study, approximately one third of subjects received pardoprunox, one third received pramipexole and one third received placebo). Prematurely withdrawn subjects from S308.3.003 study did not qualify for the extension study.

The study consisted of titration, maintenance and follow-up periods. The titration period comprised an initial double blind period of three weeks in order to bring all subjects to the dose level of 12 mg/day pardoprunox without breaking the treatment code of the S308.3.003 study. Once subjects had reached 12 mg/day pardoprunox the study continued as an open label treatment. The investigators had the possibility to adjust the dose upwards or downwards as needed within the dose range of 12 to 42 mg/day (five possible dose levels of 12, 18, 24, 30 and 42 mg/day) guided by individual safety/tolerability and efficacy over an open-label titration period of maximally four weeks. After the titration period, the study was to continue as an open-label treatment for up to 24 weeks of maintenance treatment. Prior to protocol amendment 4, the investigators had the possibility to adjust the dose upwards or downwards as needed within the dose range of 12-42 mg/day during the maintenance period, as judged by the investigator based on tolerability and efficacy. In view of protocol amendment 4 (dated 21 APR 2008) all subjects were to be down-titrated to a maximum dose of 12 mg/day (regardless of previous maintenance therapy) according to the tapering schedule for each dose level with the option for further dose reduction to 6 mg/day as judged by the investigator based on tolerability and efficacy. During maintenance, levodopa (L-dopa) was allowed to be administered as medication adjunctive to pardoprunox if the highest dose level had been reached and there was still a need for improving efficacy and in cases where further upwards adjustment of the pardoprunox dose did not bring additional benefit for the subject. At the end of the maintenance period, or if subjects terminated pardoprunox treatment for any reason prematurely, subjects entered a one week follow-up period during which pardoprunox treatment was gradually withdrawn and safety data collected.

Number of Subjects (Planned, Consented, Allocated for Treatment and Analyzed):

Planned: Between 115 and 225 subjects from the foregoing S308.3.003 study.

Consented: 202 subjects.

Allocated to treatment: 202 subjects (42 subjects in the pardoprunox-pardoprunox group, 79 subjects in the pramipexole-pardoprunox group and 81 subjects in the placebo-pardoprunox group).

Analyzed safety: 202 subjects (42 subjects in the pardoprunox-pardoprunox group, 79 subjects in the pramipexole-pardoprunox group and 81 subjects in the placebo-pardoprunox group).

Analyzed full analysis sample (FAS) sample: 199 subjects (41 subjects in the pardoprunox-pardoprunox group, 78 subjects in the pramipexole-pardoprunox group and 80 subjects in the placebo-pardoprunox group).

Diagnosis and Main Criteria for Inclusion:

Subjects who had signed informed consent for participation in this extension study and who had completed the foregoing S308.3.003 trial.

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). The dose was titrated from 12 mg/day and subjects were administered encapsulated tablets in a double blind fashion. During the open-label part of the titration and the following maintenance period, subjects were treated with doses in the range of 6-42 mg/day (protocol amendment 4, dated 21 APR 2008) and pardoprunox was administered as tablets.

Batch numbers:

Placebo capsule (matching pardoprunox capsule); batch number 70023

0.1 mg pardoprunox capsule; batch numbers 69658, 70506

0.2 mg pardoprunox capsule; batch number 69659

0.5 mg pardoprunox capsule; batch number 70316

1 mg pardoprunox capsule; batch numbers 69954, 70002, 70106

2 mg pardoprunox capsule; batch numbers 70108, 70251, 70252, 70294, 70296, 70298, 70573

4 mg pardoprunox capsule; batch number 69997, 70109, 70225, 70301, 70303, 70304, 70305, 70588, 70589

5 mg pardoprunox capsule; batch number 70110, 70258, 70308, 70420, 70594

10 mg pardoprunox capsule; batch number 69664, 70019, 70317, 70418, 70597

Duration of Treatment:

Total treatment duration was up to 31 weeks depending on the duration of the titration period (three-week fixed titration period, four-week flexible titration period and 24-week maintenance period).

Reference Therapy, Dose and Mode of Administration, Batch Number:

There was no reference therapy. Subjects were administered open label pardoprunox from the fourth titration week onwards. To maintain the blind of the foregoing S308.3.003 study, matching placebo capsules were administered to some subjects depending on the treatment group, during the first three weeks of the titration phase in a similar regimen as the active treatment.

Placebo capsules matching pardoprunox, taken orally (tid).

Placebo capsule (matching pardoprunox capsule); batch number 70023

Pramipexole (during the double-blind tapering/titration period).

0.25 mg pramipexole capsule; batch numbers 70426, 70705, 71006

0.50 mg pramipexole capsule; batch numbers 70424, 70710, 71007

0.75 mg pramipexole capsule; batch numbers 70450, 70711, 71013

Criteria for Evaluation

Efficacy:

Efficacy variable: the change from baseline to endpoint in the UPDRS motor score (UPDRS Part 3).

Other efficacy variables: the UPDRS Part 2 score, the UPDRS Part 1 score, the UPDRS, sum of Parts 2 and 3, the UPDRS, sum of Parts 1, 2 and 3, the CGI-Severity (CGI-S) and the CGI-Improvement (CGI-I), the Parkinson's Disease Questionnaire (PDQ-39) total score and the eight sub-scores, the EQ-5D total score, the Schwab and England, the modified Hoehn and Yahr and the time to start using L-dopa as concomitant medication (if applicable).

Safety:

Physical examination, vital signs assessments, standard 12-lead electrocardiogram (ECG) recording, laboratory assessments (hematology, biochemistry, urinalysis), adverse events (AEs),

concomitant medication.

Pharmacokinetics:

Plasma levels of pardoprunox were obtained for future population pharmacokinetics analyses.

Statistical Methods:

There were three groups as defined by the subject's randomized treatment group in the initial study (S308.3.003):

1. Pardoprunox-pardoprunox group consisted of subjects randomized to the pardoprunox dose group in S308.3.003 and continued in this extension study with pardoprunox.
2. Placebo-pardoprunox consisted of subjects who were randomized to placebo in S308.3.003 and continued with pardoprunox in the extension study.
3. Pramipexole-pardoprunox consisted of subjects who were randomized to pramipexole in S308.3.003 and continued with pardoprunox in the extension study.

Efficacy:

The efficacy variables were presented by descriptive statistics performed on the FAS population. No statistical testing was performed. The baseline for the extension study for all treatment groups was defined as the final visit of the preceding study S308.3.003. An additional baseline, secondary baseline, was applied as the baseline of the initial study S308.3.003, in order to highlight the changes in UPDRS Part 3 over six months (the placebo-pardoprunox group) and 12 months of active treatment (the pramipexole-pardoprunox and pardoprunox-pardoprunox groups). The use of L-dopa was summarized using frequency tables.

Safety:

All safety parameters were presented by descriptive statistics for each treatment group separately using the safety sample. Treatment emergent adverse events (TEAEs) were presented by incidence tables. Treatment-emergent AEs were defined as AEs which started at, or after, the first administration of pardoprunox during the extension study and included those events which started prior to the first administration of pardoprunox during the extension study but which worsened after the first intake. Adverse events starting after the last administration of investigational study medication but within seven days after the last intake, excluding the tapering off phase (the count of seven days following administration of investigational study medication was inclusive of the maximum duration of tapering off medication), were regarded as treatment-emergent. Non-treatment-emergent AEs included all AEs not covered by the above definition. Treatment emergent and non-treatment-emergent AEs during the study were handled equally in terms of data collection and medical management. Subjects in the pramipexole-pardoprunox group received pramipexole from Day 1 to Day 15 of the titration period so AEs that started during this time were excluded from the analysis of TEAEs. Severity and drug-event relationship of TEAEs were summarized separately. The occurrence of selected AEs was presented by time-interval.

Baseline for laboratory, vital sign and ECG parameters was defined as the baseline value from the foregoing S308.3.003 study for the pardoprunox-pardoprunox group and as the value from the final visit of the foregoing S308.3.003 study for the pramipexole-pardoprunox and placebo-pardoprunox treatment groups. Laboratory variables, including changes from baseline

were summarized. A frequency table and subject listing were presented for markedly abnormal values. Shift tables were presented according to the reference ranges (low, normal or high).

Values of vital signs and 12-lead ECG intervals, including changes from baseline, were summarized. A frequency table was presented for markedly abnormal values.

Pharmacokinetics:

Population pharmacokinetic analysis was not conducted separately for this study. The concentration data may be combined with other studies for population pharmacokinetic analysis if deemed necessary. The concentration data was only presented as listings in an appendix of this report.

Summary – Conclusions

A total of 202 subjects were allocated to treatment in this extension study, of whom 199 were included in the FAS. Three subjects were excluded from the FAS due to a lack of a post-baseline efficacy evaluation. All 202 subjects were included in the safety sample. Overall, 102 subjects prematurely withdrew from the study (11 [26.2%] subjects in the pardoprunox-pardoprunox group, 46 [58.2%] subjects in the pramipexole-pardoprunox group and 45 [55.6%] subjects in the placebo-pardoprunox group). The reasons for withdrawal were AEs (93 subjects), lack of efficacy (one subject), withdrew consent (seven subjects) and administrative (one subject).

The mean age was 60.2 years in the pardoprunox-pardoprunox group, 60.3 years in the pramipexole-pardoprunox group and 62.5 years in the placebo-pardoprunox group. A higher proportion of subjects in each group were male (53.7%, 55.1% and 61.3%, respectively). The majority of subjects were white (66.3% overall).

Efficacy Results:

The mean (standard deviation [SD]) change from baseline (defined as the final visit of the preceding S308.3.003 study) for UPDRS Part 3 at titration endpoint (OC), maintenance Week 24 (OC) and endpoint (LOCF) in the pardoprunox-pardoprunox group was -1.98 (5.56), +2.18 (7.15) and +2.12 (6.76), respectively. The mean (SD) change from baseline for UPDRS Part 3 at titration endpoint (OC), maintenance Week 24 (OC) and endpoint (LOCF) in the pramipexole-pardoprunox group was +0.45 (5.24), +1.64 (6.55) and +2.59 (6.61), respectively. The mean (SD) change from baseline for UPDRS Part 3 at titration endpoint (OC), maintenance Week 24 (OC) and endpoint (LOCF) in the placebo-pardoprunox group was -1.80 (5.80), -1.03 (7.19) and -0.23 (7.04), respectively.

Mean decreases were observed for all three treatment groups, when the values observed at each time point were compared with the secondary baseline (applied as the baseline of the foregoing S308.3.003 study, to highlight the changes in UPDRS Part 3 over six months [the placebo-pardoprunox group] and 12 months of active treatment [the pramipexole-pardoprunox and pardoprunox-pardoprunox groups]) at maintenance Week 24 (OC) and endpoint (LOCF) in the pardoprunox-pardoprunox group (-6.50 [10.85] and -5.98 [9.40], respectively), pramipexole-pardoprunox group (-6.28 [7.80] and -5.15 [8.53], respectively) and placebo-pardoprunox group (-4.77 [11.03] and -2.94 [9.62], respectively).

Small changes (both increases and decreases) from baseline to endpoint were observed in all three treatment groups for the efficacy variables: UPDRS Part 3; UPDRS Part 2; UPDRS

Part 1; UPDRS, sum of Parts 2 and 3; UPDRS, sum of Parts 1, 2 and 3; PDQ-39 (total score and sub-scores); EQ-5D; and Schwab and England ADL. Similarly, there was no notable change in the Hoehn and Yahr disease staging during the study.

The majority of subjects in each treatment group were reported with an improvement in CGI-I score at endpoint (22 [57.9%], 38 [53.5%] and 40 [52.6%] subjects in the pardoprunox-pardoprunox, pramipexole-pardoprunox and placebo-pardoprunox groups, respectively).

Most of the subjects were mildly ill at endpoint and at all assessments of CGI-S during the study. No subjects were considered to be severely ill or amongst the most extremely ill of patients.

L-dopa was administered to two (4.8%) subjects in the pardoprunox-pardoprunox group, two (2.5%) subjects in the pramipexole-pardoprunox group and three (3.7%) subjects in the placebo-pardoprunox group.

Safety Results:

The mean value for the highest study dose of pardoprunox was 31.1 mg/day in the pardoprunox-pardoprunox group, 26.4 mg/day in the pramipexole-pardoprunox group and 27.8 mg/day in the placebo-pardoprunox group.

A total of 202 subjects were included in the safety sample. One hundred and ninety-three subjects were reported with at least one TEAE during the study (39 [92.9%] subjects in the pardoprunox-pardoprunox group, 76 [96.2%] subjects in the pramipexole-pardoprunox group and 78 [96.3%] subjects in the placebo-pardoprunox group). One death occurred during the study (one [1.3%] subject in the pramipexole-pardoprunox group). The death was a result of myocardial infarction which was considered by the investigator to be unrelated to study medication. Seven subjects were reported with at least one treatment-emergent SAE (TESAE) during the study (three [7.1%] subjects in the pardoprunox-pardoprunox group, three [3.8%] subjects in the pramipexole-pardoprunox group and one [1.2%] subject in the placebo-pardoprunox group). The majority of TESAEs by preferred term (PT) were reported at the most by one subject, except for femur fracture (two subjects).

Eighty-eight subjects prematurely terminated the study due to a TEAE (eight [19.0%] subjects in the pardoprunox-pardoprunox group, 40 [50.6%] subjects in the pramipexole-pardoprunox group and 40 [49.4%] subjects in the placebo-pardoprunox group). At titration Week 7, a total of 62 subjects withdrew from the study due to AEs (five [11.9%], 29 [36.7%] and 28 [34.6%] subjects, respectively).

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	PDX-PDX (N =42)	Pramipexole-PDX (N =79)	Placebo-PDX (N = 81)
CARDIAC DISORDERS				
PALPITATIONS	n (%)	1 (2.4%)	4 (5.1%)	3 (3.7%)
EAR AND LABYRINTH DISORDERS				
VERTIGO	n (%)	2 (4.8%)	2 (2.5%)	5 (6.2%)
GASTROINTESTINAL DISORDERS				
NAUSEA	n (%)	6 (14.3%)	30 (38.0%)	43 (53.1%)
VOMITING	n (%)	2 (4.8%)	10 (12.7%)	10 (12.3%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
ASTHENIA	n (%)	2 (4.8%)	5 (6.3%)	9 (11.1%)
FATIGUE	n (%)	2 (4.8%)	4 (5.1%)	14 (17.3%)
OEDEMA PERIPHERAL	n (%)	4 (9.5%)	7 (8.9%)	6 (7.4%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS				
FALL	n (%)	0	4 (5.1%)	1 (1.2%)
NERVOUS SYSTEM DISORDERS				
BALANCE DISORDER	n (%)	3 (7.1%)	5 (6.3%)	5 (6.2%)
DIZZINESS	n (%)	4 (9.5%)	15 (19.0%)	20 (24.7%)
HEADACHE	n (%)	2 (4.8%)	6 (7.6%)	4 (4.9%)
PARAESTHESIA	n (%)	3 (7.1%)	10 (12.7%)	6 (7.4%)
SOMNOLENCE	n (%)	14 (33.3%)	24 (30.4%)	23 (28.4%)
SYNCOPE	n (%)	0	4 (5.1%)	2 (2.5%)
TREMOR	n (%)	3 (7.1%)	2 (2.5%)	1 (1.2%)
PSYCHIATRIC DISORDERS				
ABNORMAL DREAMS	n (%)	0	3 (3.8%)	5 (6.2%)
ANXIETY	n (%)	0	2 (2.5%)	6 (7.4%)
HALLUCINATION, VISUAL	n (%)	5 (11.9%)	9 (11.4%)	10 (12.3%)
INSOMNIA	n (%)	3 (7.1%)	10 (12.7%)	13 (16.0%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
HYPERHIDROSIS	n (%)	0	1 (1.3%)	5 (6.2%)
VASCULAR DISORDERS				
HYPERTENSION	n (%)	2 (4.8%)	4 (5.1%)	3 (3.7%)
HYPOTENSION	n (%)	0	2 (2.5%)	5 (6.2%)
ORTHOSTATIC HYPOTENSION	n (%)	1 (2.4%)	1 (1.3%)	6 (7.4%)

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

One hundred and eighty-four subjects were reported with newly occurring TEAEs (defined as AEs that were not reported as TEAEs for a subject in the foregoing study S308.3.003, but were

reported for the subject in the extension study). At the PT level, the most commonly reported newly occurring TEAEs reported by at least 5% of subjects in any treatment group were nausea (one [2.4%] subject in the pardoprunox-pardoprunox group, 18 [22.8%] subjects in the pramipexole-pardoprunox group and 39 [48.1%] subjects in the placebo-pardoprunox group), somnolence (eight [19.0%], 17 [21.5%] and 22 [27.2%] subjects, respectively) and dizziness (one [2.4%], 11 [13.9%] and 18 [22.2%] subjects, respectively).

The most commonly reported TEAEs by SOC were nervous system disorders (23 [54.8%] subjects in the pardoprunox-pardoprunox group, 46 [58.2%] subjects in the pramipexole-pardoprunox group and 45 [55.6%] subjects in the placebo-pardoprunox group), gastrointestinal disorders (12 [28.6%], 39 [49.4%] and 46 [56.8%] subjects, respectively) and psychiatric disorders (nine [21.4%], 26 [32.9%] and 39 [48.1%] subjects, respectively).

TEAEs related to cardiac disorders were reported in 13 subjects overall (two [4.8%] subjects in the pardoprunox-pardoprunox group, eight [10.1%] subjects in the pramipexole-pardoprunox group and three [3.7%] subjects in the placebo-pardoprunox group). The most commonly reported cardiac disorder by PT was palpitations (one [2.4%] subject in the pardoprunox-pardoprunox group, four [5.1%] subjects in the pramipexole-pardoprunox group and three [3.7%] subjects in the placebo-pardoprunox group).

The most commonly reported TEAEs considered by the Investigator to be related to study medication were nausea (five [11.9%] subjects in the pardoprunox-pardoprunox group, 29 [36.7%] subjects in the pramipexole-pardoprunox group and 41 [50.6%] subjects in the placebo-pardoprunox group) and somnolence (14 [33.3%], 23 [29.1%] and 23 [28.4%] subjects, respectively). The majority of TEAEs started during the titration period with fewer new events observed during the maintenance period.

The majority of TEAEs were mild to moderate in severity.

The most commonly reported ($\geq$ 4 subjects) severe TEAEs at the PT level were nausea (two [4.8%] subjects in the pardoprunox-pardoprunox group, three [3.8%] subjects in the pramipexole-pardoprunox group and one [1.2%] subject in the placebo-pardoprunox group) and somnolence (none, two [2.5%] and three [3.7%] subjects, respectively).

The most commonly reported events of special interest were asthenia (two [4.8%] subjects in the pardoprunox-pardoprunox group, five [6.3%] subjects in the pramipexole-pardoprunox group and nine [11.1%] subjects in the placebo-pardoprunox group), headache (two [4.8%], six [7.6%] and four [4.9%] subjects, respectively) and hypertension (two [4.8%], four [5.1%] and three [3.7%] subjects, respectively).

The most commonly reported TEAEs leading to introduction of concomitant treatment or therapy were nausea (no subjects in the pardoprunox-pardoprunox group, 10 [12.7%] subjects in the pramipexole-pardoprunox group and 15 [18.5%] subjects in the placebo-pardoprunox group), vomiting (none, three [3.8%] and six [7.4%] subjects, respectively) and hypertension (one [2.4%], three [3.8%] and two [2.5%] subjects, respectively).

The most commonly reported TEAEs leading to a dose reduction of study medication were nausea (four [9.5%] subjects in the pardoprunox-pardoprunox group, five [6.3%] subjects in the pramipexole-pardoprunox group and 11 [13.6%] subjects in the placebo-pardoprunox group), somnolence (five [11.9%], eight [10.1%] and five [6.2%] subjects, respectively), dizziness (one [2.4%], four [5.1%] and eight [9.9%] subjects, respectively) and visual hallucinations (four

[9.5%], two [2.5%] and five [6.2%] subjects, respectively).

The number 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) was low in each treatment group (one [2.4%] subject in the pardoprunox-pardoprunox group, two [2.5%] subjects in the pramipexole-pardoprunox group and two [2.5%] subjects in the placebo-pardoprunox group).

Baseline for laboratory, vital sign and ECG parameters was defined as the baseline value from the foregoing S308.3.003 study for the pardoprunox-pardoprunox group and as the value from the final visit of the foregoing S308.3.003 study for the pramipexole-pardoprunox and placebo-pardoprunox treatment groups.

No obvious changes from baseline in any quantitative laboratory parameter or qualitative urinalysis parameters were observed during the study, except in total creatine phosphokinase (CPK) which showed median increases from baseline to endpoint of +33.5 IU/L in the pardoprunox-pardoprunox group, +7.0 IU/L in the pramipexole-pardoprunox group and +18.0 IU/L in the placebo-pardoprunox group. In addition, median increases from baseline to endpoint in uric acid were observed for all three treatment groups (+18.0 mcmol/L in the pardoprunox-pardoprunox group, +6.0 mcmol/L in the pramipexole-pardoprunox group and +6.0 mcmol/L in the placebo-pardoprunox group).

Markedly abnormal high total CPK levels were reported for two (5.6%), one (1.5%) and one (1.4%) subjects in the pardoprunox-pardoprunox, pramipexole-pardoprunox and placebo-pardoprunox groups, respectively. None of these abnormalities were considered clinically significant by the Investigator. Increased blood CPK was reported as a TEAE by one (2.4%) subject in the pardoprunox-pardoprunox group and one (1.3%) subject in the pramipexole-pardoprunox group, both of which were considered clinically significant but not markedly abnormal. Blood creatine phosphokinase-muscle brain (CPK-MB) was measured in the four subjects with an abnormally high CPK level. Markedly abnormal high CPK-MB was not reported in any of the four subjects. However, one subject in the pardoprunox-pardoprunox group was reported with a TEAE of increased blood CPK-MB which was considered clinically significant but not markedly abnormal. The TEAEs of increased blood CPK and increased blood CPK-MB were all considered possibly related to the study medication. No subjects were reported with markedly abnormal alanine aminotransferase, aspartate aminotransferase or total bilirubin.

No notable changes from baseline at endpoint in vital sign parameters were observed except for some small mean changes for standing SBP and DBP and sitting SBP and DBP. For the study overall, the incidence of marked abnormalities in vital signs was low (≤ three subjects in any treatment group) except for weight. In the pardoprunox-pardoprunox group, eight (20.0%) subjects recorded a decrease of ≥ 7% in weight and 12 (30.0%) subjects recorded an increase of ≥ 7% in weight during the study. In the pramipexole-pardoprunox group, four (5.1%) subjects recorded a decrease of ≥ 7% in weight and two (2.6%) subjects recorded an increase of ≥ 7% in weight during the study. In the placebo-pardoprunox group, six (7.5%) subjects recorded a decrease of ≥ 7% in weight and three (3.8%) subjects recorded an increase of ≥ 7% in weight during the study. Overall, one (2.5%) subject in the pardoprunox-pardoprunox group, six (7.7%) subjects in the pramipexole-pardoprunox group and four (5.0%) subjects in the

placebo-pardoprunox group were reported with orthostatic hypotension during the study according to the blood pressure measurements.

Based on mean results (the average of the three ECG recordings), no subjects were reported with an average maximum QTcF or QTcB value of > 500 msec in any treatment group, one subject was reported with an average change from baseline of > 60 msec in QTcF (one [1.3%] subject in the pramipexole-pardoprunox group) and no subjects were reported with an average change in baseline of > 60 msec in QTcB in any treatment group.

Two subjects reported TEAEs relating to an abnormal ECG (one [1.3%] subject in the pramipexole-pardoprunox group and one [1.2%] subject in the placebo-pardoprunox group): non-specific intraventricular conduction delay and left axis deviation without left atrial hypertrophy. Syncope was reported as a TEAE for six subjects overall (four [5.1%] subjects in the pramipexole-pardoprunox group and two [2.5%] subjects in the placebo-pardoprunox group) and loss of consciousness was reported as a TEAE for one subject overall (one [1.3%] subject in the pramipexole-pardoprunox group).

Conclusion:

- In this extension study, subjects who continued on pardoprunox, or who switched from pramipexole to pardoprunox, from the foregoing S308.3.003 study appeared to maintain efficacy based on the UPDRS Part 3 score.
- No improvement was observed for those subjects who switched to pardoprunox in the extension study from placebo in the foregoing S308.3.003 study based on the UPDRS Part 3 score.
- Subjects titrated to pardoprunox from placebo or pramipexole reported a high incidence of AEs, a high number of dose reductions due to AEs and a high number of AEs leading to study termination, indicating that the titration was too rapid and the selected dose range (12-42 mg/day) too high in early stage PD.