2 SYNOPSIS

Sponsor/company **Orion Corporation** **Orion Pharma**	**Individual study table referring to a specific part of the dossier**	(for National Competent Authority use only)
Finished product: **Stalevo®**	**Volume:**	
Active ingredient: **Levodopa, carbidopa and entacapone**	**Page**	
Study code: 2939111		
Study title: Multicentre, randomised, double-blind study to compare Stalevo® to levodopa/carbidopa in patients with Parkinson's disease experiencing symptoms of early wearing-off		
Investigators and study centres: A total 39 centres recruited subjects in 9 countries (2 Finland, 9 Sweden, 4 Norway, 2 Denmark, 8 Germany, 1 Ireland, 5 in Latvia, 3 in Lithuania, 5 in UK)		
Development phase: IV	**Study period:** Study period: 18 Aug 2005 – 31 March 2009	
Objectives: The objectives of the study are i) to demonstrate the superiority of Stalevo® treatment to levodopa/carbidopa treatment in delaying the time from initiation of study drug until a subject requires an increase in antiparkinsonian therapy due to inadequately controlled parkinsonian symptoms ii) to study the effects of Stalevo® on subject's condition, quality of life and on subjects' plasma homocysteine level.		
Methodology: The study was a multicentre, randomised, double-blind, multinational, active-treatment controlled, parallel-group phase IV clinical study in subjects with Parkinson's disease (PD) who were currently treated with 3 equal or unequal daily doses of levodopa/dopa decarboxylase inhibitor (DDCI) and required an increase in their levodopa dosing from 3 to 4 daily doses. The eligible subjects were randomly allocated to receive either Stalevo® or levodopa/carbidopa treatment with the same individual dose strength of levodopa (mg) as taken by subject during screening period but amended by increasing the number of daily doses by one (from 3 to 4 doses). For subjects on intermediate or mixed doses; the 4 times daily dose of levodopa (mg) to be prescribed was defined in section 5.3 of the protocol. The treatment duration for an individual subject varied between a minimum of 12 months and a maximum of 24 months depending on the acquisition of primary endpoints sufficient to test the statistical hypothesis. The study consisted of a screening visit, baseline visit, 5-9 visits during treatment period and 3 mandatory telephone contacts.		
Sample size: According to the original study protocol, 244 subjects with idiopathic PD were planned to be randomised into the study: 122 subjects per treatment group. The actual number of screened subjects was 238 and 221 subjects were eligible for the study: 115 subjects in Stalevo group and 106 in levodopa/carbidopa group.		
Diagnosis and main criteria for inclusion: **Diagnosis:** Patients with idiopathic Parkinson's disease requiring an increase in their levodopa dosing from 3 to 4 daily doses. **Main criteria for inclusion and exclusion:** **Inclusion:** • Male or female patients • Patients with idiopathic Parkinson's disease and end-of-dose motor-fluctuations not stabilized on their current levodopa/DDCI treatment • Hoehn&Yahr (H&Y) stage 1-3 performed during the "ON" state • Treatment with 3 equal or unequal daily doses of standard-release levodopa/DDCI up to a maximum		

total daily levodopa dose of 450 mg. • Unchanged levodopa/DDCI and other antiparkinsonian medication (amantadine, monoamine oxidase B inhibitor (MAO-B) with an approved dose, anticholinergics and/or dopamine agonists), if any, for at least 6 weeks prior to baseline visit • Age: 30 years or above **Exclusion:** • Secondary or atypical parkinsonism • Patients with daily unpredictable "OFF"-periods or painful dyskinesia (including painful dystonia) • Previous or current treatment with a COMT inhibitor • Current treatment with controlled-release or extended-release levodopa/DDCI preparations except one evening (8-12pm) dose of a CR levodopa preparation to control night time symptoms is allowed. • Patients requiring rescue medication (including soluble levodopa formulations)
Investigational product, dose and mode of administration: Stalevo® (levodopa/carbidopa/entacapone). The following oral dosage strengths were used: 50 mg: 50/12.5/200 mg capsules (batch numbers: 1065074, 1125794 and 1208819) and 100 mg: 100/25/200 mg capsules (batch numbers: 1070786, 1148741 and 1217596), and 150 mg: 100/25/200 mg capsules (batch numbers: 1070786, 1148741 and 1217596) + levodopa/carbidopa 50/12.5 mg capsules (batch numbers: 1065074, 1125794 and 1208819).
Duration of treatment: The minimum treatment period per subject was 12 months and the maximum treatment period was 24 months.
Reference product, dose and mode of administration: Levodopa/carbidopa. The following oral dosage strengths were used: 50 mg: 50/12.5 mg capsules (batch numbers: NE20240, NG29310, and NA50910), 100 mg: 100/25 mg capsules (batch numbers: NA50000, NE08040 and NG34190), and 150 mg: 100/25 mg capsules (batch numbers: NA50000, NE08040 and NG34190) + 50/12.5 mg capsules (batch numbers: NE20240, NG29310, and NA50910).
Variables and methods of assessments: Primary efficacy variable: Primary efficacy variable was the time from initiation of study drug until the subject requires an increase in antiparkinsonian therapy due to inadequately controlled parkinsonian symptoms, i.e. an increase in daily levodopa dose, an increase in levodopa dosing frequency, an increase in other antiparkinsonian therapy and/or an initiation of another antiparkinsonian therapy. The need for additional antiparkinsonian therapy was judged by the investigator. Secondary efficacy variables: Secondary efficacy variables were Unified Parkinson's Disease Rating Scale (UPDRS) Parts I-IV (assessed at the same time of day at each visit, 3 hours after the subject's previous dose of study drug), Investigator's Clinical Global Impression of Change (CGI-C), Parkinson's Disease Questionnaire (PDQ-39) for the assessment of quality of life (self-administered by the subject) and work impairment due to PD, assessed by a specially designed work impairment questionnaire (WIQ). Safety assessments: Safety assessments included: Laboratory assessments (haematology and clinical chemistry), measurement of vital signs, 12-lead electrocardiogram (ECG), physical examination and adverse events (AEs). Assessments of homocysteine: Plasma homocysteine test were performed at screening and at month 12.
Statistical methods: Primary efficacy variable: Cox's proportional hazards model was utilised. Hazard ratio with 95% confidence intervals was estimated for treatment difference in time to an increase in antiparkinsonian therapy. Primary efficacy evaluation was repeated using the log-rank statistics to test difference between treatments. Kaplan-Meier (KM) curves by treatment groups was drawn to visualise the effect of the treatment. Secondary efficacy variables: The scores of the UPDRS were calculated at baseline and at each visit; parts I-IV separately and the sum of

scores from parts I-III and II-III together. The difference in total sum of scores of the UPDRS were compared between treatment groups from all visits to baseline (visit 1) by repeated analysis of covariance (ANCOVA) using linear mixed effect model.
The frequencies of subjects in the original 7 categories of CGI-C were calculated. CGI-C was analysed by frequency table after transforming the original categories yielding the outcomes 'improvement' or 'no improvement' at visits 4 and 6. The categories CGI-C were compared between treatment groups with Cochran-Mantel-Haenszel method.
PDQ-39 was analysed similarly to UPDRS at visits 4, 6 and 10.
Total Work Impairment (TWI) percentage, the Proportion of work days missed (WDM) and the Average Work Productivity Impairment (WPI) percentage when working were analysed by subject and treatment group at visits 1, 3, 4, 5, 6 and 10. Descriptive statistics were provided on all 3 measures in the population employed.
Homocysteine and safety assessments:
The concentration of plasma homocysteine was compared between treatment groups from visit 6 to screening by ANCOVA using linear mixed effect model.
Demographics and vital signs were reported descriptively.
AEs were classified using Medical Dictionary for Regulatory Activities (MedDRA) in accordance with Orion Pharma MedDRA coding rules. Contingency tables for each event including subject's study number, the severity of the symptoms and the causal relationship to study treatment were provided.

Summary-Conclusions

Demography and other baseline characteristics: The study population (N=221) consisted of mainly Caucasian (99.5%) females and males. The mean age was 69.5 (range 43-91) years. The mean duration (SD) of PD was similar in both treatment groups 4 (3.1) years. The mean H&Y stage score was 2.1 with the majority of the subjects at Stage 2 (40.7%) or at Stage 2.5 (25.3%). The mean total UPDRS score for parts II-III at screening was 35.3 points in the Stalevo group and 32.8 points in the levodopa/carbidopa group. 8.7% of subjects in the Stalevo group and 16.4% in the levodopa/carbidopa group were employed at baseline.

Efficacy results:

Primary efficacy variable:

The primary variable of the study, an increase in antiparkinsonian therapy due to inadequately controlled parkinsonian symptoms was reached by 48 out of 115 (41.7%) and 54 out of 106 (50.9%) subjects in the Stalevo and levodopa/carbidipa groups, respectively.

The hazard ratio between the treatment groups was 0.76 (95% CI 0.51 – 1.12; p = 0.167) which translates into a 24% reduction in the rate of primary endpoints for the subjects randomised to the Stalevo group. Log-rank statistics performed as supportive analyses confirmed the results (p = 0.228). Judging from the Kaplan-Meier curve, the difference between the treatment groups emerged after 9 months of treatment, when the survival rates start to differentiate in favor of the Stalevo treated subjects. The median time to increase in PD medication was 23.7 months in the Stalevo treated subjects and 20.5 months in the levodopa/carbidopa treated subjects, and the time until 25% of the subjects reached the primary endpoint 11.7 months (95% CI 6.9-16.5) and 8.3 months (95% CI 6.5-14.7), respectively.

For subjects treated with concomitant DAs the time to increase dopaminergic medication was clearly shorter than in those subjects not receiving concomitant DAs. Time until 25% of the subjects on DAs reached the endpoint was 6.9 months (95% CI 3.0-11.8) and 6.5 months (95% CI 3.2-9.0) in the Stalevo and levodopa/carbidopa groups, respectively. In subjects without DAs, these times were 16.7 months (95% CI 11.8-23.6) and 14.7 months (95% CI 7.4-18.7), respectively. The hazard ratios between the treatment groups were similar for the subjects with and without DAs.

For subjects with H&Y stage $\geq$ 2.5 the hazard ratio between the treatment groups was 0.58 (95% CI 0.32-1.07) favoring Stalevo and approaching statistical significance (p = 0.080). Hazard ratio between the treatment groups in subjects with H&Y stage $\leq$ 2 was 0.90 (95% CI 0.53-1.54) with a p-value of 0.710. Previous DDCI before the randomisation carbidopa or benserazide, did not have effect on the hazard ratio between the treatment groups.

Secondary efficacy variables:

There were no statistically significant differences in the overall mean change from baseline between the treatment groups even though the mean improvements from baseline in UPDRS III scores were numerically greater for Stalevo treated subjects compared to levodopa/carbidopa treated. The differences in UPDRS Q32, Q33 or Q39 questions, assessing duration of and disability due dyskinesia and off-time were not statistically significant.

Altogether 68 (72.3%) and 49 (57.0%) subjects in the Stalevo group showed an improvement in the CGI-C assessed by the investigator at month 6 and 12, respectively, compared with 63 (67.0%) and 43 (54.4%) in the levodopa/carbidopa group, indicating a small but non-significant ($p = 0.429$ at 6 months and $p = 0.743$ at 12 months) benefit for Stalevo.

In addition, there was no difference between the treatments in quality of life as assessed by the mean change from baseline in the PDQ-39 or PDQ-8 index score or any individual item. Neither were statistically significant differences seen between the treatments at individual question level. As only 27 subjects (12.2%) were employed at baseline, the evaluation of the Work Impairment Questionnaire (WIQ) results was not feasible.

Safety results:

One or more AEs were experienced by more subjects in the Stalevo group (84.3%) compared to the levodopa/carbidopa group (71.7%). Chromaturia, nausea and diarrhoea were the most frequently reported AEs, and occurred more often in the Stalevo group (16.5%, 14.8% and 13.0%, respectively) compared with the levodopa/carbidopa group (3.8%, 6.6% and 3.8%, respectively). Also dyskinesia and hypertension were more often reported in the Stalevo group (both 7.0%) compared with the levodopa/carbidopa group (both 2.8%).

There were 2 subjects with myocardial infarction/acute myocardial infarction and 1 acute coronary syndrome in the Stalevo group and none in the levodopa/carbidopa group The 2 subjects with myocardial infarction had underlying ischaemic heart disease/myocardial infarction or coronary artery disease reported at baseline. The third subject with acute coronary syndrome had cerebrovascular impairment and poor peripheral perfusion.

The percentage of the subjects who experienced AEs that were judged to be study drug related was higher in the Stalevo group (53.9%) compared to levodopa/carbidopa group (30.2%). The most common AEs with positive causality were chromaturia (16.5% and 2.8%), nausea (10.4% and 4.7%), diarrhoea (8.7% and 1.9%) and dyskinesia (7.0% and 2.8%, respectively for Stalevo and levodopa/carbidopa).

There were very few severe AEs, and they occurred somewhat more often in the levodopa/carbidopa group (n = 18) compared to Stalevo group (n = 11).

There were 2 deaths in the levodopa/carbidopa group compared to none in the Stalevo group. The percentage of the subjects experiencing SAEs were comparable between Stalevo and levodopa/carbidopa groups (20.0% vs. 17.9%).

A higher percentage of the subjects in the Stalevo group compared to levodopa/carbidopa group experienced AEs leading to discontinuation of the study (15.7% vs. 6.6%), AEs leading to discontinuation of the study treatment (13.0% and 5.7%), and AEs leading to dose reduction (5.2% and 1.9%).

Vital signs, ECG, laboratory safety measurements and physical examinations indicated no safety concerns.

No difference between the treatments was seen in plasma homocysteine levels (change from screening).

Conclusion:

The population in this study represented relatively early PD patients with recently emerged wearing-off symptoms. At randomization, subjects in both treatment groups increased their daily levodopa dose by about 30% increasing the dosing frequency at the same time from 3 to 4. This is probably why many efficacy parameters showed marked improvements also with levodopa/carbidopa during the first 6-9 months and why the differences in the need to increase PD medication started to emerge only after a relatively long follow-up. It can be concluded that the assumptions made in the sample size calculation underestimated the efficacy of

levodopa/carbidopa in the chosen study population and design. The results of the primary endpoint indicated however that there was a clinically meaningful difference (although being statistically non-significant) in the number of endpoints favouring Stalevo. The benefit of Stalevo also seemed to be greater in subjects with more advanced disease. Overall, the results of this study are in line with previous studies showing that symptomatic efficacy of Stalevo/entacapone compared to levodopa/DDCI is better in more advanced disease compared to earlier PD population.

Like in STRIDE-PD, there was an imbalance in subjects with myocardial infarction (3 subjects on Stalevo vs none on levodopa/carbidopa). Otherwise no unexpected safety issues were seen.

Date of report: 5 Oct 2009