2. SYNOPSIS

Sponsor/company Orion Corporation Orion Pharma	**Individual study table referring to a specific part of the dossier** **Volume:** **Page**	(for National Competent Authority use only)
Finished product: Not applicable		
Active ingredient: Levodopa, carbidopa and entacapone		

Study code: 2939136

Study title: Duration of motor response after administration of experimental levodopa/carbidopa/entacapone treatment regimens compared to standard treatment (Stalevo®); a randomised, double-blind, crossover, multicentre, single dose study in patients with Parkinson's disease and wearing-off symptoms

Investigators and study centres: The study was conducted at 7 centres, 3 centres in Sweden and 4 in Finland. The coordinating investigator was Vilho Myllylä, ODL Terveys Oy, Oulu, Finland.

Development phase: IIa

Study period: 10 Mar 2011-25 Jul 2011

Objectives: The primary objective was to assess the effect of a single dose of two experimental levodopa/carbidopa/entacapone (L/C/E) treatment regimens versus standard L/C/E treatment regimen in Parkinson's disease (PD) patients with end-of-dose motor fluctuations in terms of duration of motor response after the first morning dose of levodopa.

The secondary objective was to evaluate the safety of the L/C/E treatment regimens in patients with PD.

Methodology: This was a randomised, double-blind, 3-period crossover study comparing the effects of a single dose of 2 L/C/E treatment regimens (A and B) and standard L/C/E treatment regimen (Stalevo) on the duration of motor response in PD patients with wearing-off symptoms after the first morning dose of levodopa.

The study consisted of a screening visit, 3 treatment visits and an end-of-study visit. Within 14 days of the screening visit, the patients received a single morning dose of study drug (either of the 2 L/C/E treatment regimens) or Stalevo. The order of the 3 treatment periods was randomised according to a crossover design and the duration of each period was 2 days, followed by a wash-out period (1-9 days) during which the patients were on their individual standard PD treatment.

Before each study day, patients arrived at the study centre in the previous evening. The patients' own standard PD treatments was discontinued at the latest by 22:00 and continued after completion of the motor part (part III) of the Unified Parkinson's Disease Rating Scale (UPDRS III) next day. After completion of the UPDRS III, patients returned to their own standard PD treatments.

Duration of the study was 2 to 7 weeks per patient, depending on the length of the screening and wash-out periods.

Sample size The planned number of subjects was 27 (3-6 subjects per centre). 28 subjects were randomised and included in the intention-to-treat (ITT) data set. The per-protocol (PP) data set included 27 subjects. There were 2 discontinuations, thus 26 subjects completed the study.

Diagnosis and main criteria for inclusion:

Inclusion criteria:

1. Written informed consent (IC) obtained.
2. Male or female patients with idiopathic PD according to the United Kingdom brain bank criteria with end-of-dose motor fluctuations
3. Hoehn and Yahr stage 2-4 performed during the "ON" state.

4. Duration of response between 1.5 and 4 hours (based on medical history) to the patient's first morning dose of levodopa/dopa decarboxylase inhibitor (DDCI) with or without entacapone.
5. Treatment with 3-8 daily doses of levodopa/DDCI with or without entacapone with a total daily levodopa dose in the range of 300-1200 mg. One evening dose of controlled-release formulation of levodopa/DDCI was allowed provided that it was included in the total of 3-8 daily doses of levodopa/DDCI mentioned above.
6. Unchanged levodopa/DDCI with or without entacapone and other antiparkinsonian medication (dopamine agonists, monoamine oxidase [MAO] B inhibitor, amantadine and/or anticholinergics with approved doses), if any, for at least 6 weeks prior to the screening visit.
7. Age of 30 years or above.

Exclusion criteria:

1. Secondary or atypical parkinsonism.
2. Use of tolcapone within 6 weeks prior to the first treatment period.
3. Previous tolerability problems with entacapone or tolcapone.
4. Concomitant treatment with apomorphine, MAO-A inhibitors or non-selective MAO inhibitors.
5. Concomitant treatment with drugs having antidopaminergic action including alpha-methyldopa, reserpine and antipsychotic drugs (also D2 receptor blocking antiemetics except domperidone). As an exception, an evening dose of an atypical antipsychotic was allowed.
6. Use of any iron preparations.
7. Intensity of dyskinesias which would have, in the opinion of the investigator, interfered with the interpretation of the UPDRS III scoring during the levodopa challenge test.
8. Currently active hallucinations.
9. Severe orthostatic hypotension as judged by the investigator.
10. Mini-Mental State Examination (MMSE) score < 26.
11. History of neuroleptic malignant syndrome (NMS) and/or non-traumatic rhabdomyolysis.
12. Past or current treatment with deep brain stimulation (DBS) or other surgical treatment for PD.
13. Treatment with levodopa or dopamine agonist infusion or injection.
14. Active malignancy, narrow-angle glaucoma or pheochromocytoma.
15. Clinically significant cardiovascular, pulmonary, gastrointestinal, hepatic, renal, neurological or psychiatric disorder or any other major concurrent illness that in the opinion of the investigator would have interfered with the interpretation of the study results or constituted a health risk for the subject if he/she had taken part into the study.
16. Alanine aminotransferase or aspartate aminotransferase > upper limit of normal at screening.
17. Any other abnormal value of laboratory, vital signs or electrocardiogram (ECG) which would in the opinion of the investigator have interfered with the interpretation of the study results or caused health risk for the subject if he/she had taken part into the study.
18. Female patients of childbearing potential (i.e. menstruating or less than 2 years postmenopausal) if they were not using proper contraception (hormonal contraception, intrauterine device [IUD] or surgical sterilisation, spermicidal foam in conjunction with condom on male partner).
19. Patients with pre-planned elective surgery.
20. Known hypersensitivity to active substances or to any of the excipients of the study drugs.
21. Participation in a drug study within 60 days prior to entry to this study.

Any other condition that in the opinion of the investigator would have interfered with the interpretation of the study results or constituted a health risk for the subject if he/she had taken part into the study.

Investigational product, dose and mode of administration, batch numbers:

- Stalevo® 100/25/200 mg film-coated tablets (containing 100 mg of levodopa, 25 mg of carbidopa and 200

mg of entacapone) (batch number: 169121)

- Stalevo® 150/37.5/200 mg film-coated tablets (containing 150 mg of levodopa, 37.5 mg of carbidopa and 200 mg of entacapone) (batch number: 1367984)
- Carbidopa 20 mg (batch number: MK005L1) and 27.5 mg capsules (batch number: MK006L1)
- Placebo for carbidopa 20 mg capsules (MK004L1)

Carbidopa/placebo capsules were administered first, followed by a Stalevo (100 or 150 mg) tablet 45 minutes later. The levodopa dose in Stalevo (100 or 150 mg) was the dose that was nearest to the patient's standard individual levodopa pre-randomisation dose. All study drugs were ingested with 200 ml of tap water. Patients were to maintain a sitting or standing position (and move around), but not a supine position, for at least 2 hours after administration of Stalevo, if possible.

Patients received during the treatment regimen A period 1 Stalevo 100 tablet and 4 carbidopa 20 mg capsules, or 1 Stalevo 150 tablet, 2 carbidopa 20 mg capsules and 1 carbidopa 27.5 mg capsule), and during the treatment regimen B period 1 Stalevo 100 tablet and 2 carbidopa 20 mg capsules, 2 placebo for carbidopa 20 mg capsules, or 1 Stalevo 150 tablet and 1 carbidopa 27.5 mg capsule and 2 placebo for carbidopa 20 mg capsules.

Duration of treatment: The single doses of the investigational and reference products were taken in a 3-period, crossover design.

Reference product, dose and mode of administration, batch numbers:

- Stalevo® 100/25/200 mg film-coated tablets (batch number: 169121)
- Stalevo® 150/37.5/200 mg film-coated tablets (batch number: 1367984)
- Placebo for carbidopa 20 and 27.5 mg capsules (MK004L1)

Placebo for carbidopa capsules was administered first, followed by a Stalevo (100 or 150 mg) tablet 45 minutes later. Mode of administration was identical to that of the investigational products (see above).

Patients received during the treatment regiment C period 1 Stalevo 100 and 4 placebo for carbidopa 20 mg capsules, or Stalevo 150, 2 placebo for 20 mg carbidopa capsules and 1 placebo for 27.5 mg carbidopa capsule.

Variables and methods of assessments:

Primary efficacy variable

- Duration of motor response to levodopa ("ON"-time), as determined using the UPDRS III. The start of the response was defined as when the UPDRS III score showed a 10% reduction from the baseline, and it was considered to have ended when the UPDRS III score returned to within 10% of the baseline. UPDRS III was assessed twice, 20 minutes apart, after administration of the carbidopa/placebo capsules but before administration of Stalevo. After administration of Stalevo, UPDRS III was assessed at every 20 minutes until the patient had turned "OFF" or up to a maximum of 6 hours.

Other efficacy variables

- Magnitude of clinical response (mean baseline UPDRS III score - the lowest UPDRS III score)
- Time to reach the lowest UPDRS III score
- Responder ('ON'-time lasting ≥ 3 hours) analysis
- UPDRS III from baseline to 6 hours as a continuous variable by repeated measures analysis of covariance (ANCOVA)
- Presence and intensity of dyskinesia was assessed at every 20 minutes after UPDRS III scoring.

Safety variables

- Adverse events (AEs) throughout the study.
- Supine and orthostatic (supine to standing) heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP) at screening and end-of-study.
- A 12-lead ECG after 10 minutes at rest at screening and at end-of-study.
- Physical examination at screening and end-of-study.

Laboratory safety assessments (haematology, clinical chemistry and urine analyses) at screening and end-of-study.

Statistical methods:

The primary objective of the study was evaluated using duration of motor response determined by UPDRS III. A total sample size of 27 the study had 80% power to detect a difference in UPDRS III means of 35 minutes (the difference between treatment regimen A of 175 minutes and standard Stalevo of 140 minutes with a 0.05 two-sided significance level).

Statistical method for the primary comparison was analysis of variance (ANOVA) with the following grouping factors: treatment, sequence, subject and period. Differences between Stalevo and treatment regimen A were evaluated using orthogonal contrasts with 5% significance level.

Statistical methods for the lowest UPDRS III score was ANCOVA with the following grouping factors: treatment, sequence, subject, baseline and period. Time to reach the lowest UPDRS III score was analysed with the same methods as the primary evaluation. UPDRS III was analysed using repeated measures ANCOVA with the following grouping factors baseline, period, treatment, rating time and subject.

"ON"-time lasting up to 3 hours or more was considered as a clinically significant response, which was analysed using McNemar's test. Presence of dyskinesias was analysed using McNemar's test and severity of dyskinesias was tabulated.

Summary-Conclusions

Demography and other baseline characteristics:

Study subjects were Caucasian male (n = 16) and female (n = 12) PD patients with a mean age of 62.5 years. The mean daily levodopa dose was 594 mg (standard deviation [SD] 254) and the mean number of daily levodopa doses 5.0 (SD 1.6).

Efficacy results:

Primary efficacy variable - duration of motor response after first morning dose of levodopa (ITT population):

A trend of carbidopa dose response favouring the 105 mg dose was seen after the study periods 1 and 2. However, during the study period 3 the mean duration of motor response was highest on Stalevo and lowest on 105 mg of carbidopa, and thus no statistically significant difference was found between the mean durations of motor response for the 3 periods (p = 0.596 and 0.475 for difference between treatment A or B and Stalevo, respectively). The estimated mean duration of motor response after the first morning dose of levodopa was 150 min with 105 mg dose of carbidopa, 136 min with 65 mg of carbidopa and 144 min with Stalevo.

Other efficacy variables:

No statistically significant difference in the lowest UPDRS III score, time to reach the lowest UPRDS III score, or magnitude of clinical response between the investigational treatment A or B and Stalevo was seen. Neither were statistically significant differences seen in responders between the investigational treatments and Stalevo. Fewer subjects with treatment A (65.4%) and B (67.9%) reported having dyskinesia compared to those with Stalevo (74.1%). The differences were, however, not statistically significant (p = 0.157 and 0.317 for treatment A and B, respectively).

Safety results:

Vital signs, ECG, laboratory safety measurements and physical examinations indicated no safety concerns. Altogether 5 AEs were reported after the start of the study treatment. 2 subjects experienced an SAE (anxiety and pneumonia) leading to permanent discontinuation of the study treatment. None of the AEs was judged to be study drug related.

Conclusion: A trend of carbidopa dose response favouring the 105 mg dose was seen after the study periods 1 and 2. However, the same pattern was not seen during study period 3 and the study failed to show a significant carbidopa dose response in the duration of ON-time after the first morning dose of levodopa (L/C/E). The 2 investigational L/C/E regimens containing 65 and 105 mg of carbidopa were equally well tolerated and safe compared with Stalevo in this single dose study.

Date of report: 22 Dec 2011