SYNOPSIS

Sponsor/Company **Orion Corporation** **Orion Pharma**	**Individual study table referring to a specific part of the dossier** **Volume:** **Page**	(for National Regulatory Authority use only)
Finished product: Stalevo 200		
Active ingredient: Levodopa 200mg/carbidopa 50mg and entacapone 200 mg		

Study code: 2939121

Study title: Effects of single doses of Stalevo 200 and levodopa/carbidopa 200/50 mg on striatal ^{11}C-raclopride binding potential in Parkinson's disease patients with wearing-off symptoms. An open, randomised, active-controlled, two-period crossover study.

Investigators and study centres: Coordinating Investigator Juha Rinne, Clinical Research Services Turku (CRST), Turku; Seppo Kaakkola, M.D., Helsinki University central Hospital, Meilahti Hospital, Helsinki; Vilho Myllylä, M.D., Oulu University Hospital, Oulu.

Development phase:	**Study period:**
II	3 Dec 2007 (first subject screened) - 27 Mar 2008 (last subject last visit)

Objectives: The primary objective of the study was:

- to compare the effect of Stalevo 200 and Sinemet on the change of striatal (putaminal and caudate) ^{11}C-raclopride binding potential (BP) from baseline in Parkinson's disease (PD) patients with wearing-off symptoms.

The secondary objective of the study was:

- to compare the effects of Stalevo 200 and Sinemet on levodopa mean concentrations between 2.5 – 3.5 h ($C_{2.5\text{-}3.5}$).

Additional objectives of the study were:

- to determine C_{max}, t_{max} and $AUC_{0\text{-}4h}$ of levodopa,
- to evaluate the relationship between striatal (putaminal and caudate) ^{11}C-raclopride BP and the Unified Parkinson's Disease Rating Scale (UPDRS) part III scoring after Stalevo 200 and Sinemet administrations, and
- to evaluate the relationship between striatal (putaminal and caudate) ^{11}C-raclopride BP and levodopa mean $C_{2.5\text{-}3.5h}$ after Stalevo 200 and Sinemet administrations, and
- to evaluate the relationship between striatal (putaminal and caudate) ^{11}C-raclopride BP and levodopa challenge test after Stalevo and Sinemet administrations
- safety of the study drugs was evaluated.

The study, however, was terminated after 6 subjects, based on interim results. The analyses planned in the clinical study protocol are modified accordingly.

Methodology: This was an open, randomised, active-controlled, 2-period crossover study comparing the effect of single doses of Stalevo 200 and Sinemet on striatal (putaminal and caudate) ^{11}C-raclopride BP in PD patients with wearing-off symptoms. The study consisted of 4 visits: a screening visit (visit 1), 2 treatment periods (period 1=visit 2, period 2=visit 3) separated by a minimum wash-out period of at least 3 days, and an end-of-study visit (visit 4). Subjects were randomly allocated to start the period 1 with a single dose of Stalevo 200 or Sinemet. After wash-out the study drug on period 2 was administered according to a crossover design. Duration of the study was approximately from 3 to 14 weeks per study subject, depending on the length of the

screening and wash-out periods.

Sample size: Planned: A total of 14-16 subjects were planned to be recruited into the study. **Actual:** A total of 8 subjects were screened and 6 enrolled.

Diagnosis and main criteria for inclusion:

Inclusion criteria:

1. Male or female patients with idiopathic Parkinson's disease according to the UK Brain Bank criteria.
2. Predictable wearing-off symptoms with a response to standard release levodopa/carbidopa (200/50 mg) during the levodopa challenge test lasting for a minimum of 1.5 h and a maximum of 4 h.
3. The magnitude of response (peak effect) in the levodopa challenge test is at least 30%. The magnitude of response is defined to be the difference between the baseline score and the lowest UPDRS III score during the levodopa challenge test.
4. Hoehn and Yahr stage of at least 2.0 performed during the 'ON' state.
5. Treatment with at least 4 daily doses of levodopa/dopa decarboxylase inhibitor (DDCI) (± entacapone (Comtess® or Stalevo) with total daily levodopa dose in the range of 400-1200mg.
6. Unchanged levodopa/DDCI ± entacapone and other antiparkinsonian medication [dopamine agonists, monoamine oxidase B (MAO-B) inhibitor, amantadine and/or anticholinergics with an approved dose], if any, for at least 2 weeks prior to period I.
7. Written informed consent obtained.
8. Age of 45-80 years, inclusive.

Investigational drug, dose and mode of administration: 1 tablet of Stalevo 200 (levodopa 200 mg, carbidopa 50 mg, entacapone 200 mg) orally, manufactured by Orion Corporation, Orion Pharma, Espoo, Finland.

Duration of treatment: Single doses of the investigational and comparative study drugs were taken in cross-over design 2.5 h before the post dosing PET scans.

Comparative drug, dose and mode of administration: 2 tablets of Sinemet 100/25 mg (levodopa 100 mg, carbidopa 25 mg) orally, manufactured by MSD, purchased in Finland.

Variables and methods of assessments:

Primary efficacy variable:

The difference between the study drugs in change in striatal (putaminal and caudate) ^{11}C-raclopride BP. Striatal (putaminal and caudate) ^{11}C-raclopride BP will be determined with PET scans performed at baseline and during the time period from 2.5 to 3.5 h after the study drug administration.

Secondary efficacy variable:

The difference between the study drugs in levodopa mean $C_{2.5-3.5h}$.

Pharmacokinetic variables:

For levodopa pharmacokinetics (PK) frequent blood samples were collected at the earliest 15 minutes (min) before the study drug administration and 20 min, 40 min, 60 min, 90 min, 120 min, 150 min (2.5 h), 165 min, 180 min, 195 min, 210 min (3.5 h), and 240 min after the study drug administration.

The following parameters were determined:

$C_{2.5-3.5}$	mean levodopa concentration on the time points between 2.5 – 3.5 h
C_{max}	maximum observed concentration
t_{max}	time to reach the maximum observed concentration
AUC_{0-4}	area under the concentration-time curve from zero to 4 hours

Additional variables:

The difference between the study drugs in change in UPDRS part III scores determined prior to the study drug intake and immediately after the post dosing PET scanning 3.5 h after the study drug administration.
The difference between the study drugs in $C_{max,}$ t_{max} and AUC_{0-4h} of levodopa.

The relationship between striatal (putaminal and caudate) ^{11}C-raclopride BP and plasma levodopa mean $C_{2.5\text{-}3.5h}$. Data from period 1 and period 2 was pooled for this analysis.

The relationship between striatal (putaminal and caudate) ^{11}C-raclopride BP and UPDRS part III scoring. Data from period 1 and period 2 was pooled for this analysis.

Safety and tolerability variables:

Laboratory safety variables (taken in a fasting state) at screening were : Haemoglobin, haematocrit, erythrocyte count, leucocyte count, platelet count, mean corpuscular volume, mean corpuscular haemoglobin, creatinine, alkaline phosphatase, alanine aminotransferase, gamma-glutamyl transferase, sodium, potassium, f-glucose, C-reactive protein, urine analysis; screening for illicit drugs (amphetamine, barbiturates, cannabinoid, cocaine, and methadone), urine pregnancy test for females of childbearing potential. The same laboratory determinations that were performed at screening (with the exception of screening for illicit drugs) were repeated at the end-of-study visit. Physical examination, 12-lead ECG and vital signs were determined at screening and at the end of study. Adverse events (AEs) and medical history, concomitant diseases and concomitant treatments were reported continuously during the study.

Evaluation and statistical methods: The change in the striatal (putaminal and caudate) ^{11}C-raclopride BP from baseline and levodopa PK was planned to be evaluated between Stalevo 200 and Sinemet after 3-6 subjects had completed period 1 and period 2. Thereafter, a go/no-go decision to continue the study with possible re-estimation of the sample size was to be done.

Primary variable: The statistical method used for the primary evaluation was parametric analysis of covariance (ANCOVA). Treatment, sequence, period and baseline were included in the model as fixed effects. Patient and error term were modelled as random effects. In case of non-normality of residuals, transformation or non-parametric method was considered. There was no aim to detect certain statistically significant difference.

Secondary variables: The secondary objective of the study was to evaluate levodopa mean $C_{2.5\text{-}3.5}$ between Stalevo 200 and Sinemet. The statistical method used for the primary evaluation was parametric analysis of variance (ANOVA). Treatment, sequence, and period were included in the model as fixed effects. Patient within sequence and error term were modelled as random effects. There was no aim to detect certain statistically significant difference.

Additional variables:

The C_{max}, t_{max} and $AUC_{0\text{-}4h}$ of levodopa were evaluated by descriptive statistics.

The relationship between striatal ^{11}C-raclopride BP and the UPDRS scoring after Stalevo 200 and Sinemet administrations was evaluated.

The relationship between striatal ^{11}C-raclopride BP and levodopa mean $C_{2.5\text{-}3.5h}$ after Stalevo 200 and Sinemet administrations was evaluated.

AEs reported during the study were classified by system organ classes (SOCs) and preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA) coding system. The AEs were displayed in a frequency table by period. The number and proportion (%) of subjects having each symptom, severity of these symptoms (mild, moderate, severe) and causality to Stalevo 200 or Sinemet were given. Serious AEs (SAEs) and those AEs which lead to discontinuation of the treatment, significant additional therapy or other significant concomitant treatment were evaluated case by case. AEs occurring before and after the initiation of study treatments were reported separately.

Clinical safety evaluations: Vital signs including heart rate (HR) and blood pressure (BP) (sitting position) and

12-lead ECG (normal/abnormal) performed at screening and end-of-study visit were tabulated using descriptive statistics. Results of physical examination were tabulated using frequency tables.

Laboratory safety evaluations: Laboratory safety variables were tabulated using descriptive statistics. All the clinically significant values were listed.

SUMMARY OF RESULTS

This abbreviated report report consists of data from 6 subjects (subjects 101-106). 5 subjects completed both study periods including PET scans.

Efficacy results:

Primary efficacy variable:

In subjects 103 and 105 the ^{11}C-raclopride BP (putamen sum and caudate nucleus sum) decreased when compared to the BP before dosing of Stalevo 200. After Stalevo 200, the highest decrease was detected in subject 105 with a BP changes of -0.45 (putamen sum) and -0.12 (caudate nucleus sum). In subjects 102, 104 and 106 the BP increased after Stalevo 200 treatment. At baseline the binding potential was comparable between the treatment periods.

Secondary efficacy variable:

The levodopa mean concentrations at 2.5-3 hours (periods 1 and 2 pooled) were 954 ng/ml (SD 359) for Stalevo 200 and 617 ng/ml (SD 302) for Sinemet. The individual values for Stalevo 200 ranged from 555.0 to 1391 ng/ml and for Sinemet from 304.4 to 1079 ng/ml.

Additional variables:

Pharmacokinetic variables:

The mean C_{max} (periods 1 and 2 pooled) was 2072 ng/ml (SD 549) for Stalevo 200 and 1886 ng/ml (SD 827) for Sinemet. The individual C_{max} values for Stalevo 200 ranged from 1590 to 3120 ng/ml, and for Sinemet from 938 to 3300 ng/ml.

The mean AUC_{0-4h} (periods 1 and 2 pooled) was 4510 ng*h/ml (SD 1408) for Stalevo 200 and 3477 ng*h/ml (SD 1400) for Sinemet. The individual AUC_{0-4h} values for Stalevo 200 ranged from 3064 to 6464 ng*h/ml and for Sinemet from 2320 to 6043 ng*h/ml.The median t_{max} (periods 1 and 2 pooled) was 1 h for both Stalevo 200 (SD 0.2) and Sinemet (SD 0.3). Individual t_{max} values ranged from 1 to 1.5 h for Stalevo 200 and from 0.67 to 1.5 h for Sinemet.

Relationship between striatal ^{11}C-raclopride BP and the UPDRS scoring:

In all subjects, except subject 101, UPDRS III scores decreased when compared to the scores determined before dosing of Stalevo 200. In subjects 103, 104 and 106, the UPDRS III scores decreased more after the dosing of Stalevo 200 than Sinemet. No statistically significant correlation was detected between ^{11}C-raclopride BP in putamen (sum) or caudate nucleus (sum) and UPDRS III scores after Stalevo 200 or Sinemet.

Relationship between striatal ^{11}C-raclopride binding potential and levodopa mean C2.5-3.5h:

No statistically significant correlation was detected between striatal 11C-raclopride BP and the levodopa mean C2.5-3.5h after Stalevo 200 or Sinemet.

Relationship between striatal ^{11}C-raclopride binding potential and levodopa challenge test:

The mean duration of ON-time was 120 min (SD 30) both during Stalevo 200 and Sinemet treatments. No significant correlations were detected between the ^{11}C-raclopride BP and the levodopa challenge test in different regions of striatum.

Safety results:

3 subjects (50.0%) reported a total of 11 AEs. All reported AEs were mild in severity. 5 AEs were reported as related to the treatment. No deaths, other SAEs or other significant AEs were reported. No clinically relevant changes were reported in laboratory parameters, heart rate, blood pressure, physical examination or 12-lead ECG in any of the subjects.

Conclusions:

During the interim review it was concluded that the ^{11}C-raclopride binding results were highly variable and inconsistent. This was probably due to technical reasons (e.g. head movements during PET imaging) and possible insensitivity of the used method to find differences between the 2 levodopa products.

According to the protocol, ^{11}C-raclopride imaging (lasting for 1h) was started in this study 2.5 h after the study drug administration in all subjects. However, in 3 subjects, the drug response (ON-time) ended already 2.5 hours after the administration of levodopa/carbidopa 200/50 mg in the levodopa challenge test performed at screening. This might explain some of the unexpected results.

Assuming that the seen variability of the results would not have been changed during further subjects, re-estimation of the sample size would not have helped reaching the original assumptions. Therefore, continuing in this situation included also potential ethical issues, because the protocol was regarded very demanding for the wearing-off patients. Taking all the above into consideration, a no-go decision was made and the study was discontinued prematurely.

There is probably no single reason to explain all the inconsistencies seen in the ^{11}C-raclopride binding results in this study. However, if similar future studies will be planned to study levodopa-induced changes in the ^{11}C-raclopride binding, timing of the PET scans according to individual response durations of levodopa (determined by levodopa challenge test) should be considered.

Date of report: 23 Dec 2008