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: 2939135

Study title: Efficacy and safety of ODM-101 compared to a standard combination (Stalevo®); a randomised, double-blind, crossover, proof of concept study in patients with Parkinson's disease and end-of-dose motor fluctuations

Investigators and study centres:

This study was conducted in 5 countries (24 study centres): Germany (7), Finland (5), Latvia (4), Lithuania (3), and Romania (5).

The coordinating investigator was Prof Claudia Trenkwalder, Paracelsus-Elena-Klinik, Kassel, Germany

Development phase: II	**Study period:** 31 May 2011 - 07 Aug 2012 (first patient first visit - last patient last visit)

Objectives: The primary objective of the study was to assess the efficacy, carbidopa dose response and safety of ODM-101, a new combination of levodopa, carbidopa and entacapone in the treatment of Parkinson's disease (PD) patients with end-of-dose motor fluctuations.

The secondary objectives of the study were to obtain initial data on switching patients from levodopa/dopa decarboxylase inhibitor (DDCI) with or without entacapone directly to ODM-101, to determine the size of the therapeutic effect and to study levodopa daily dose and dosing frequency of the combination.

Methodology:

This was a randomised, double-blind, double-dummy, active-controlled, crossover, multicentre, phase II proof of concept study in patients with PD and end-of-dose motor fluctuations. The patient's individually optimised daily levodopa regimen was kept stable for at least 2 weeks before randomisation. The patients were randomised to receive ODM-101 with 65 mg of carbidopa (ODM-101/65), ODM-101 with 105 mg of carbidopa (ODM-101/105), and Stalevo® according to a 3-period crossover design. At each dosing, the patient received ODM-101/65 or ODM-101/105 and corresponding placebo for Stalevo®, or Stalevo® and corresponding placebo for ODM-101; a total of 2 tablets.

The study consisted of a screening period, 3 treatment periods of 4 weeks each, and a post-treatment period. For each patient, there were 9 visits: a screening visit performed 7-28 days before randomisation, a randomisation visit (visit 1), 6 visits during the 3 treatment periods (i.e. 2, 4, 6, 8, 10 and 12 weeks after randomisation and the start of the study treatment; visits 2-7), and an end-of-study visit 7-21 days after the last visit of the last treatment period. The duration of study was 14-23 weeks for each patient.

After the screening period, eligible patients were randomised and switched to study drugs after all assessments had been performed at visit 1. The strength of the levodopa in the study drug (75, 100, 125 or 150 mg) was determined by the patient's individually optimised levodopa regimen established before randomisation. During the first 2 weeks of each treatment period, the patient's levodopa strength (but not frequency) was adjusted as necessary by the investigator. For the remaining 2 weeks of each treatment period, the levodopa strengths were to be kept stable.

Unscheduled visits could be performed during the first 2 weeks of each treatment period if there was a need to adjust the levodopa strength.

Sample size:

The planned number of patients according to the statistical power analysis was approximately 100 and the actual number of patients randomised was 117.

Diagnosis and main criteria for inclusion:

Inclusion criteria:

- Written informed consent (IC) obtained.
- Male or female patients with idiopathic PD according to the UK brain bank criteria with end-of-dose motor fluctuations.
- Hoehn and Yahr stage 2-4 performed during the ON state.
- An average of ≥ 3.0 hours of OFF-time, with a minimum of 0.5 hours of OFF-time on each day (using PD home diary [hereafter diary]) on 3 consecutive days before the decision of entry.
- Treatment with 3-8 regular daily doses of levodopa/DDCI with entacapone (either levodopa/DDCI combined with Comtess®/Comtan® or as Stalevo®) or without entacapone, including daily use of a soluble levodopa formulation, with a total daily levodopa dose in the range of 400-1400 mg. One evening dose of controlled-release formulation of levodopa/DDCI was allowed providing it was included in the total daily levodopa dose in the range of 400-1400 mg mentioned above. Use of additional soluble levodopa formulations as rescue treatment, such as Madopar LT or Quick, up to a maximum of 4 doses per week was allowed; however, its use was to be avoided on days when PD status (diary) was recorded. The levodopa dose from these rescue soluble levodopa formulations was not included in the range of total regular daily dose of levodopa indicated above. (Expansion of permitted regular daily dose frequency of PD medications from 4-8 to 3-8, permitted daily total levodopa dose from 400-1200 mg to 400-1400 mg, and inclusion of regular daily use of soluble levodopa formulations in these calculations, as well as exceptions to switching rules and definition of rescue added in protocol amendment 1, 03 Jan 2012.)
- Unchanged levodopa/DDCI with or without entacapone and other anti-parkinsonian medication (dopamine agonists, monoamine oxidase [MAO] B inhibitor, amantadine and/or anticholinergics with doses recommended by the manufacturer), if any, for at least 4 weeks prior to the screening visit.
- Age of 30 years or above.

Exclusion criteria:

- Secondary or atypical parkinsonism.
- Current use of tolcapone (within 6 weeks prior to the first treatment period).
- Previous tolerability problems with entacapone or tolcapone.
- Concomitant treatment with apomorphine, MAO-A inhibitors or non-selective MAO inhibitors.
- Concomitant treatment with drugs having antidopaminergic action including alpha-methyldopa, reserpine and antipsychotic drugs (also dopamine D2 receptor blocking antiemetics except domperidone). As an exception to the prohibition of use of antipsychotic drugs, 1 evening dose of an atypical antipsychotic was allowed.
- Severe dyskinesias as judged by the investigator; however, mild to moderate dyskinesia not significantly affecting patient's activities of daily living was allowed.
- Current active hallucinations.
- Severe orthostatic hypotension as judged by the investigator.
- Current dementia (Mini-Mental State Examination [MMSE] score < 24).
- Problematic impulse control disorders such as pathological gambling, hypersexuality or compulsive shopping within 6 months prior to the screening visit.
- History of neuroleptic malignant syndrome (NMS) and/or non-traumatic (drug-induced) rhabdomyolysis. ("Drug-induced" added in protocol amendment 1, 03 Jan 2012.)
- Past or current treatment with deep brain stimulation or other surgical treatment for PD.

- Narrow-angle glaucoma or pheochromocytoma.
- Any active malignant cancer.
- Patients with pre-planned elective surgery that was likely to change or impact on the control of PD symptoms, or involve hospitalisation. (Change or impact etc. added in protocol amendment 1, 03 Jan 2012).
- Failure to demonstrate acceptable/appropriate use of the diary, despite adequate training, during the screening visit or other separate training sessions during the screening period.

Investigational product, dose and mode of administration, batch number(s):

ODM-101 was supplied as fixed triple (levodopa/carbidopa/entacapone) combination tablets for oral administration. The levodopa dose in each formulation was 75, 100, 125 or 150 mg. The carbidopa dose in each formulation was 65 or 105 mg. Each tablet contained 200 mg of entacapone. In total, there were 8 different test formulations. Batch numbers: 1373105, 1373106, 1375497, 1375501, 1373107, 1373108, 1375499 and 1375500.

The placebo tablets for ODM-101 were indistinguishable from the investigational product. Batch numbers: 1368240 and 1368241.

Duration of treatment: 12-16 weeks

Reference product, dose and mode of administration, batch number(s):

The levodopa/carbidopa/entacapone combination tablets (Stalevo®) containing 75, 100, 125 or 150 mg of levodopa and 18.75, 25.0, 31.25 or 37.5 mg of carbidopa were used as an active comparator. Each Stalevo® tablet contained 200 mg of entacapone. Batch numbers: 1369111, 1369011, 1369114 and 1375346.

The placebo tablets for Stalevo® were indistinguishable from the reference product. Batch numbers: 1368058, 1368186, 1368063 and1368065.

Variables and methods of assessments:

Primary efficacy variable:

PD status was recorded by using a diary. The patient (or a care giver on behalf of the patient) recorded whether the patient was OFF, ON without dyskinesia, ON with non-troublesome dyskinesia, ON with troublesome dyskinesia, or asleep, in 30-minutes time slots ("except during sleep time" deleted in protocol amendment 1, 03 Jan 2012) for 3 consecutive days before randomisation and for 3 consecutive days, starting 26 (+6) days after visits 1, 3 and 5 (i.e. weeks 0, 4 and 8). The OFF-time recorded by the diary was used as the primary efficacy variable. An electronic patient diary was used from the beginning of the study but an option to use a paper patient diary was also allowed during the study.

Secondary efficacy variables:

- Unified Parkinson's Disease Rating Scale (UPDRS) I-IV at randomisation (i.e. week 0) and at weeks 4, 8 and 12 as assessed by the investigator.
- Schwab and England Activities of Daily Living (ADL) scale as assessed by the investigator at randomisation (i.e. week 0) and at weeks 4, 8 and 12 by the investigator.
- Presence of dyskinesia was calculated using diary data.
- Total daily levodopa dose and the number of daily doses at each visit was calculated.
- Proportion of responders was calculated using diary data.

Other variables:

- Feasibility of the use of electronic PD home diary (hereafter eDiary)

Safety variables:

Safety was assessed by adverse events (AEs), heart rate (HR), supine and orthostatic systolic (SBP) and diastolic blood pressure (DBP), electrocardiogram (ECG), physical examination and laboratory safety assessments. Suicidality was assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS). Presence of sleep attacks during the treatment period was assessed using an investigator administered questionnaire. (Assessment of sleep attacks added in protocol amendment 1, 03 Jan 2012.)

Statistical methods:

The duration of daily ON-time without troublesome dyskinesia, ON-time without dyskinesia, ON-time with troublesome and non-troublesome dyskinesia, OFF-time, or asleep, as measured by the diary, was analysed using an analysis of variance (ANOVA) model for crossover design. The model included treatment, period, and sequence as exploratory variables. The primary evaluation was performed for the change from baseline in OFF-time.

UPDRS I-IV and the sum of UPDRS II and III ('total score') were analysed using ANOVA, and Schwab and England ADL scale was analysed using an analysis of covariance (ANCOVA) model for a crossover design.

The presence of dyskinesia (ON with/without dyskinesia, ON with/without non-troublesome dyskinesia) was analysed using McNemar's test.

The total daily dose of levodopa and the number of daily doses were analysed using an ANOVA model for a crossover design.

Patients were defined as responders when OFF time decreased from baseline by1 hour or more (cut-point 1), 3 hours or more (cut-point 2) and by 30% or more (cut-point 3). Responder analysis was performed using repeated measures logistic regression. In addition to comparing the 3 treatments with each other, the responder analysis was also evaluated after the first treatment period only.

Feasibility of the use of the electronic PD home diary (hereafter eDiary) was analysed using descriptive statistics.

The AEs (as event counts and patient counts) were displayed in a frequency table. The number and proportion (%) of patients having each AE, severity of AEs and causality to the drug were given. Serious adverse events (SAEs) and other significant AEs were evaluated case by case. The absolute values and changes from baseline (i.e. visit 1) in HR, SBP and DBP and 12-lead ECG variables were summarised using descriptive statistics. The interpretation of ECG (i.e. normal/abnormal) was tabulated. Abnormal physical examination findings, laboratory safety variables, suicidality and sleep attacks were summarised using descriptive statistics. (Assessment of sleep attacks added in protocol amendment 1, 03 Jan 2012.)

Summary-Conclusions

Demography and other baseline characteristics:

117 patients were randomised into the study and comprised the safety population. 101 patients (86.3%) completed all 3 cross-over treatment periods (cross-over analysis), and 111 patients (94.9%) completed the first treatment period (first period analysis). Table 1 summarises demographics and other baseline characteristics.

Table 1. Demographics and other baseline characteristics

ITT population (N = 116)	Total
Sex (Female/Male)	44%/56%
Age (Years), mean (SD)	67.0 (9.6)
Caucasian, n (%)	116 (100)
Duration of PD (Years), Mean (SD)	9.0 (4.6)
Duration of OFF (h), Mean (SD)	5.3 (2.4)
UPDRS II, mean (SD)	10.7 (6.1)
UPDRS III, mean (SD)	21.3 (13.3)
Hoehn & Yahn, mean (SD)	2.6 (0.5)
Safety population (N = 117)	
Levodopa dose (mg), Mean (SD)	611.5 (192.7)
Number of levodopa doses, mean (SD)	4.8 (1.1)
MAO-B inhibitor use, n (%)	47 (40.2)
Dopamine agonist use, n (%)	95 (81.2)

Efficacy results:

Primary efficacy analysis

Mean OFF-time decreased with all 3 treatments and significantly more with ODM-101 than with Stalevo®. In the cross-over analysis, the mean changes from baseline in OFF-time were -1.58 hours after treatment with ODM-101/65 (n=107), -1.35 hours after treatment with ODM-101/105 (n=110), and -1.00 hours after treatment with Stalevo® (n=110). The differences between the treatments were statistically significant for ODM-101/65 vs Stalevo® (difference of -0.59 hours, p = 0.017) but not for ODM-101/105 vs Stalevo® (difference of -0.37 hours, p = 0.127). A significant carry-over effect was observed in the cross-over analysis (p = 0.048) and the analysis was performed with a predefined adjustment for a first order carry over effect. The differences in the mean changes from baseline in OFF-time for ODM-101/65 vs Stalevo® of -0.62 hours and between ODM-101/105 vs Stalevo® of -0.65 hours were statistically significant (p = 0.021 and p = 0.015, respectively).

For parallel group comparison, a preplanned analysis was performed of patients who completed the first treatment period (first period analysis). In this analysis, the mean changes from baseline in OFF-time were: -1.32 hours after treatment with ODM-101/65 (n=37), -1.23 hours after treatment with ODM-101/105 (n=36), and -0.74 hours after treatment with Stalevo® (n=38). The differences in the mean changes from baseline in OFF-time for ODM-101/65 vs Stalevo® of -0.555 hours and between ODM-101/105 vs Stalevo® of -0.731 hours were not statistically significant as the study was not powered for this analysis (p = 0.288 and p = 0.167, respectively).

Secondary efficacy analysis (cross-over population)

Mean ON-time without troublesome dyskinesia increased by more than 1 hour with all 3 treatments. The differences between the treatments in the mean changes from baseline with carry-over adjustment were close to statistical significance for the comparison ODM-101/65 vs Stalevo® (+0.56 hours, p = 0.053) and was statistically significant for the comparison ODM-101/105 vs Stalevo® (0.63 hours, p = 0.033).

The differences between the treatments in mean changes from baseline with carry-over adjustment in ON-time with no dyskinesia were statistically significant for the comparisons ODM-101/65 vs Stalevo® (+0.84 hours, p = 0.005) and for ODM-101/105 vs Stalevo® (+0.69 hours, p = 0.021). The mean changes from baseline in ON-time with troublesome dyskinesia were close to zero with all 3 treatments, and the differences between the treatments in the mean changes from baseline with carry-over adjustment were not statistically significant (+0.02 hours for ODM-101/65 vs Stalevo® [p = 0.916] and +0.10 hours for ODM-101/105 vs Stalevo® [p = 0.535]). The differences between the treatments in mean changes from baseline with carry-over adjustment in ON-time with non-troublesome dyskinesia were not statistically significant (-0.29 hours for ODM-101/65 vs Stalevo® [p = 0.147] and -0.08 hours for ODM-101/105 vs Stalevo® [p = 0.691]).

Mean UPDRS scores for parts II and III combined (measured while ON) decreased with all 3 treatments. The differences between the treatments in the mean changes from baseline in the combined scores of the UPDRS parts II and III were not statistically significant for the comparisons ODM-101/65 vs Stalevo® (-0.679, p = 0.390) and for ODM-101/105 vs Stalevo® (-0.751, p = 0.346).

Schwab and England ADL scores were unchanged in most patients at the end of each treatment period. However, improvements occurred in a numerically higher proportion of patients after ODM-101/65.

Patients were defined as responders when OFF time decreased from baseline by 1 hour or more (cut-point 1), 3 hours or more (cut-point 2) and by 30% or more (cut-point 3). The proportions of responders with ODM-101/65, ODM-101/105, and Stalevo® were, respectively, 51.0%, 52.8%, and 48.6% at cut-point 1; 24.0%, 24.5%, and 24.3% at cut-point 2; and 46.2%, 47.2%, and 37.4% at cut-point 3. The differences between the treatments were not statistically significant at any of the cut-points.

Safety results:

A total of 265 AEs were reported by 79 patients (67.5%) during any treatment period: 42 patients (38.2%) patients reported 87 AEs during ODM-101/65 treatment, 52 patients (46.0%) reported 95 AEs during ODM-101/105 treatment, and 36 patients (32.7%) reported 83 AEs during Stalevo® treatment. The most common preferred terms for AEs were nausea (16 patients, 13.7%), followed by dizziness (12 patients, 10.3%),

headache and drug effect decreased (10 patients, 8.5% each), dyskinesia (9 patients, 7.7%), and diarrhoea and insomnia (7 patients, 6.0% each). AEs were mild in 61 patients (52.1%), moderate in 39 patients (33.3%) and severe in 6 patients (5.1%). Severe AEs were reported in 3 patients (2.7%) during ODM-101/65 treatment (dyskinesia, back pain, fall, traumatic haematoma, restless legs syndrome, and nausea), 3 patients (2.7%) during ODM-101/105 treatment (bradykinesia, insomnia, and myocardial infarction), and by 1 patient (0.9%) during Stalevo® treatment (pain in extremity).
59 patients (50.4%) had 157 treatment-related AEs: 30 patients (27.3%) reported 55 treatment-related AEs with ODM-101/65, 30 patients (26.5%) reported 43 treatment-related AEs with ODM-101/105, and 27 patients (24.5%) reported 59 treatment-related AEs with Stalevo®. The most common treatment-related AEs were nausea (8 patients, 7.3%, ODM-101/65; 1 patient, 0.9%, ODM-101/105; 3 patients, 2.7%, Stalevo®), followed by dizziness (4 patients, 3.6%, ODM-101/65; 3 patients, 2.7%, ODM-101/105; 3 patients, 2.7%, Stalevo®), drug effect decreased (3 patients, 2.7% of patients with each treatment), and dyskinesia (1 patients, 0.9%, ODM-101/65; 5 patients, 5.3%, ODM-101/105; 2 patients, 1.8%, Stalevo®). One patient (0.9%) died during treatment period 2 (ODM-101/105). The cause of death was cardiorespiratory arrest due to myocardial infarction, and was considered not related to study medication.
A total of 8 patients (6.8%) experienced 12 SAEs, including the 2 SAEs by the patient who died. SAEs that were considered treatment related were: diarrhoea (ODM-101/105), and myocardial ischaemia, blood CK increased, and diarrhoea (Stalevo®). The SAEs that were not considered treatment-related were back pain (ODM-101/65), cataract operation followed by surgery to correct a complication, and bronchospasm (ODM-101/105), and hypertension (Stalevo®). In addition, 1 patient experienced an SAE of ON and OFF phenomenon 11 days after the last dose of study medication. 10 patients (8.5%) were discontinued from study medication: 5 patients were discontinued from treatment with ODM-101/65 (due to anxiety [2 cases], fall, drug effect decreased, and nausea), 4 patients were discontinued from ODM-101/105 (due to bradykinesia, dyskinesia, diarrhoea, and death), and 1 patient was discontinued from Stalevo®, (due to myocardial ischaemia). 8 patients (6.8%) had AEs that led to dose reduction; 2.7% of patients with each treatment. The reasons for dose reductions were dyskinesia [2 cases], and hypersomnia (ODM-101/65), dyskinesia [2 cases], and tension (ODM-101/105), and insomnia, hallucination, dizziness, rapid eye movements sleep abnormal, and disorientation (Stalevo®). The frequency and severity of AEs was higher with ODM-101 than with Stalevo® and was higher with ODM-101/105 than with ODM-101/65. There were no clinically meaningful changes from baseline in mean laboratory variables, vital signs or ECG data, although small differences between the treatments were observed. 1 patient had clinically significant abnormal alanine aminotransferase and aspartate aminotransferase values during treatment period 1 with ODM-101/65. The corresponding AEs were considered treatment-related. No action was taken, the patient continued in the study, and no further clinically significant abnormalities were observed for this patient. All clinically significant abnormal findings in laboratory variables, vital signs or ECG were reported as AEs.

Conclusions:

The present study showed that ODM-101 is potentially a more effective levodopa treatment compared with Stalevo® in PD patients with motor fluctuations symptoms. ODM-101/65 was the lowest effective ODM-101 strength (in terms of carbidopa), as there were no differences in general in efficacy between the two strengths. Considering the efficacy results and the tolerability and safety of both ODM-101 combinations in this study, ODM-101 and especially ODM-101/65 is worth studying further in large phase III studies.

- ODM-101/65 and 105 were more effective than Stalevo® in reducing mean daily OFF-time in PD patients with end-of-dose motor fluctuations.
- ODM-101/65 and 105 were more effective than Stalevo® in increasing mean daily ON-time without troublesome dyskinesia.
- There were no differences between the treatments in ON-time with troublesome dyskinesia.
- Overall, there were no differences in efficacy when assessed as changes of ON- and OFF-time between the two carbidopa strengths in ODM-101.
- There were no statistically significant differences between the treatment in UPDRS II and III scores or Schwab and England ADL scores.
- The increase in the occurrence of psychiatric and general symptoms of depression, anxiety and asthenia during ODM-101/105 and muscle, musculoskeletal and connective tissue pain during both ODM-101 carbidopa strengths should be further studied in future clinical studies. The risk/benefit ratio was considered acceptable for all of the treatments.

Date of report: 28 March 2013