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# Patient satisfaction with switching to Stalevo: an open-label evaluation in PD patients experiencing wearing-off (Simcom Study)

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*Objectives and methods* – This study investigated the ease with which 52 Parkinson's disease patients already receiving adjunct entacapone to traditional levodopa were switched to Stalevo® (levodopa/carbidopa/entacapone). *Results* – The switch to Stalevo was straightforward for most patients taking standard-release levodopa with 86% of these patients being able to replace their entire regimen without having to change the amount of levodopa taken. The majority of patients (54%, $P = 0.162$) preferred Stalevo; 31% preferred their prior treatment regimen; 15% had no preference. Patients found Stalevo more simple to dose (94%), more convenient to use (84%), easier to handle (84%), easier to remember (67%) and easier to swallow (59%), compared with their previous medication. *Conclusions* – Stalevo was well tolerated, with a low incidence of adverse events. The study shows that Stalevo is an effective, preferred and well-tolerated means of delivering levodopa/carbidopa/entacapone in one easy-to-use tablet.

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Since its introduction, levodopa has remained unrivalled in its symptomatic efficacy for the management of idiopathic Parkinson's disease (PD) (1, 2). Indeed, despite the large number of novel agents that have been developed, the majority of patients still depend on levodopa because of its superior efficacy over other antiparkinsonian therapies (2, 3). However, due to its short half-life, long-term levodopa use is frequently associated with the emergence of motor complications, such as wearing-off and dyskinesia (4, 5). All major advances to levodopa therapy over the past four decades have therefore been driven by the need to deliver a more consistent long-term therapeutic response to levodopa, without the development of treatment-associated complications.

Since the 1970s, levodopa has been routinely administered with a dopa-decarboxylase inhibitor (DDCI), such as carbidopa or benserazide, to reduce its peripheral metabolism and increase its uptake into the brain. When levodopa is combined with a DDCI, its metabolism is shifted to the catechol-*O*-methyl transferase (COMT) metabolic pathway. Thus, when the COMT inhibitor – entacapone – is included in the levodopa regimen, the elimination half-life of levodopa/carbidopa is further increased by 85%, from 1.3 to 2.4 h (6–9). As entacapone has similar $T_{max}$ and half-life values as levodopa, it can be administered in combination with each levodopa dose to enhance the bioavailability of levodopa (10). The enhanced levodopa bioavailability that is achieved via co-administration of entacapone has been proved in several prospective studies to reduce 'off' time and increase 'on' time in PD patients with motor fluctuations (11–15). These benefits have been shown to persist in long-term trials where patients have been assessed for up to 3 years (16). In addition, two

of the trials have also observed significant improvements in disability and activities of daily living (ADL) in non-fluctuating patients (14, 15).

Collectively, the results from these studies suggest that the use of entacapone with traditional levodopa/DDCI regimens permits patients to reduce their levodopa dose and enjoy enhanced motor responses for extended periods of time, regardless of whether or not they are experiencing fluctuations at treatment initiation. Separate studies also confirm that a combination product (levodopa/DDCI/entacapone; Stalevo®; Orion Corporation, Orion Pharma, Espoo, Finland) should behave in a bioequivalent manner with respect to pharmacokinetics and pharmacodynamics, as seen when levodopa/DDCI plus entacapone is taken together, while at the same time affording better delivery of levodopa and greater convenience (17). To that end, Stalevo is a new and optimized levodopa product that contains the traditional treatment regimen of levodopa/DDCI (carbidopa) in combination with entacapone in one oral formulation.

The aim of the present study was to assess the impact of switching from traditional levodopa/DDCI therapies with adjunctive entacapone therapy to Stalevo. Stalevo is available in the three most frequently prescribed dose combinations of levodopa/DDCI and entacapone so that a switch can be made from traditional levodopa/DDCI therapies to Stalevo with ease. Although previous studies in patients with PD have established the safety profile of levodopa/carbidopa and entacapone taken separately, at the time that this study was performed the safety and tolerability of this new formulation was based on bioequivalence to its separate components in healthy subjects (18). It is therefore crucial to examine any issues that may arise when switching from separate components to one formulation. In addition, patient preference for traditional levodopa/DDCI plus entacapone vs Stalevo therapy was investigated.

## Materials and methods

A total of 52 patients were enrolled in the study. All patients gave prior, written informed consent, and the study procedures were performed in accordance with the principles of the Declaration of Helsinki. Inclusion criteria were: idiopathic PD, age 35–75 years, currently receiving standard-release levodopa/DCCI (carbidopa or benserazide) plus entacapone, three to six times daily (with a stable dosing regimen maintained for at least 1 month prior to the study). Patients with symptomatic parkinsonism or unpredictable 'off' periods or painful dyskinesia were excluded. In addition, patients with a history or any signs of clinically significant renal or hepatic disease, or other significant concurrent illness or abnormal laboratory value that could influence the outcome of the study, were excluded. Current treatment with non-selective mono-amine oxidase (MAO) inhibitors, simultaneous use of MAO-A and MAO-B inhibitors, alpha-methyldopa, reserpine, neuroleptics, any agents with anti-dopaminergic action, rimiterol, isoprenaline, adrenaline, noradrenaline, dopamine, dobutamine or apomorphine was prohibited. The use of the selective MAO-B inhibitor selegiline was allowed up to 10 mg/day. Finally, one dose of controlled-release levodopa was allowed for night-time symptomatic control.

This single-group, open, crossover, phase III multicentre study was carried out at six centres in Finland. The study consisted of three consecutive periods: a 4-week control period during which patients continued their usual levodopa/DDCI and entacapone regimen, a 4-week treatment phase during which patients received Stalevo at the most appropriate dose and a 2-week follow-up period, when each patient returned to his/her own previous levodopa/DDCI and entacapone treatment (see Fig. 1). The Stalevo dose that patients received during the treatment phase was selected by the investigator to correspond as closely as possible to

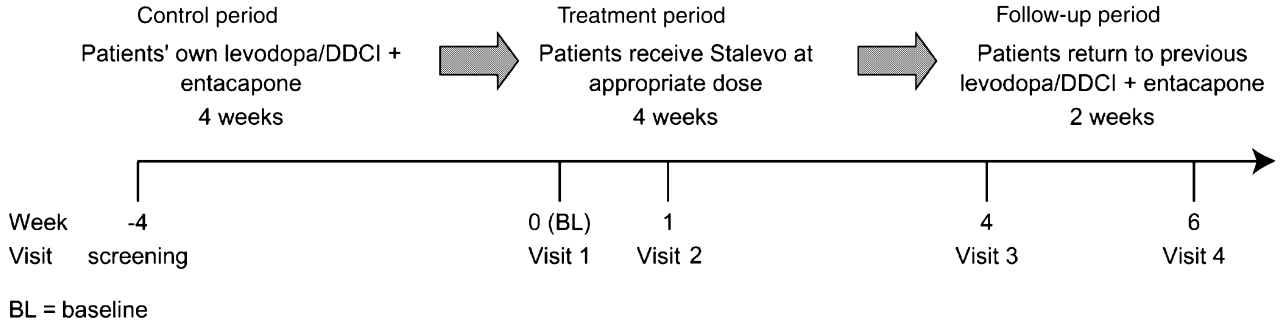


**Figure 1.** Study design.

each patient's levodopa dose during the control period.

Two data sets were defined for the purpose of the statistical analysis; the intention-to-treat (ITT) data set and the per protocol (PP) data set. The ITT populations comprised the data set for the efficacy analysis and included all the patients who received at least one dose of the study treatments and recorded at least one baseline measurement of the efficacy variable in question. The PP data set included all those patients who completed the study and did not experience any major violations of the protocol.

Patient preference for treatment was the primary efficacy variable and was assessed at the end of study treatment. Patients evaluated their preference based on whether they preferred to continue their treatment with Stalevo (study treatment), or with separate tablets (previous treatment), or observed no difference between these two treatments. The patients were also questioned on which of the treatments (separate tablets or Stalevo tablets) was easier to remember, easier to handle, more simple to dose, easier to swallow and more convenient. In addition, any changes to the Stalevo dose initially selected by the investigator were recorded. The frequency of patient preference to treatment was calculated for the ITT population, and missing assessments were estimated by the worst case option (previous treatment) if the investigator believed the reason for discontinuation was related to the test treatment.

Secondary efficacy parameters included treatment success rate, assessed by both the investigator's and the patient's global impression of change in the patient's overall clinical condition compared with the control period. The patient's clinical condition was evaluated in the 'on' stage using the Unified Parkinson's Disease Rating Scale (UPDRS) at baseline and at the end of the treatment phase with Stalevo. Mean daily levodopa dose and frequency of dosing were calculated from patient diaries. Patients assessed their quality of life during the previous treatment (separate tablets) and with the Stalevo treatment on a visual analogue scale (VAS).

Safety evaluations were carried out at Week 1 and at the end of the treatment period at Week 4. The safety population consisted of all study patients who received at least one dose of study treatment ($n = 52$). Safety assessments included monitoring of adverse events (AEs) and vital signs at every visit. Laboratory variables (haematology and biochemistry), including liver function tests, were measured and electrocardiograms (ECGs) were recorded only at screening visit for exclusion purposes, as there are currently no regulatory recommendations for the monitoring of any laboratory parameter or ECGs during entacapone treatment.

## Results

The baseline characteristics of the patients in the ITT and PP populations were comparable and are summarized in Table 1. To further demonstrate the practicalities of switching from levodopa plus entacapone to Stalevo, a single case study is also presented (Table 2).

**Table 1** Baseline characteristics of the patients in the intent-to-treat (ITT) and per protocol (PP) populations

| Parameter | Safety and ITT population ($n = 52$) | PP population ($n = 45$) |
|---|---|---|
| Sex | | |
| Female, *n* (%) | 17 (33) | 14 (31) |
| Male, *n* (%) | 35 (67) | 31 (69) |
| Age, mean ± SD (years) | 61.3 ± 8.4 | 62.0 ± 8.5 |
| Age at onset of PD (years) | 52.7 ± 9.6 | 53.4 ± 9.8 |
| Duration of PD (years) | 9.2 ± 4.1 | 9.2 ± 4.4 |
| Duration of levodopa treatment (years) | 8.2 ± 4.3 | 8.1 ± 4.5 |
| Number of levodopa doses per day ± SD | 4.8 ± 1.5 | 4.6 ± 1.3 |
| Duration of entacapone treatment (years) | 2.2 ± 1.9 | 2.0 ± 1.7 |

PD, Parkinson's disease.

**Table 2** Case study

| | |
|---|---|
| 64-year-old male | |
| Diagnosed with PD for 11 years, old myocardial infarction, anaemia present (treated with continuous ferrous aspartate), impotence present (treated with 25 or 50 mg sildenafil, as needed), parosmia due to PD | |
| Previous medication | 900 mg total daily levodopa<br>Levodopa/carbidopa 100/25 (6 times daily); levodopa controlled-release (100 mg once daily); levodopa/benserazide dispersible 100/25 (1/2 tablet, 4 times daily); entacapone (6 times daily)<br>Total: 17 tablets (2 × 6 plus 4 plus 1)/day |
| Study medication | |
| Week 1 | 700 mg total daily levodopa; Stalevo 100/25/200 mg (4 times daily) plus 150/37.5/200 mg (2 times daily)<br>Total: 6 tablets (1 × 6)/day |
| Weeks 2–4 | 650 mg total daily levodopa; Stalevo 100/25/200 mg (5 times daily) plus 150/37.5/200 mg (1 time daily)<br>Total: 6 tablets (1 × 6)/day |
| Adverse events | Yes; dyskinesia and neck and head pain with dyskinesia, occurred during week 1 of study treatment<br>Action taken: dosage reduced<br>Resolved: no |
| Treatment preference | |
| Overall | Study treatment |
| Treatment comparisons | |
| Easier to remember | Study treatment |
| Easier to handle | Study treatment |
| More simple to dose | Study treatment |
| Easier to swallow | Study treatment |
| More convenient | Study treatment |

Four of 56 screened patients were excluded, the reasons being age ($n = 1$), dementia ($n = 1$) and use of more than one daily dose of controlled-release levodopa ($n = 2$). Of the 52 patients who entered the study and who were included in the ITT population, four (8%) prematurely discontinued the study treatment: three (6%) due to an AE, and one because he wished to continue his previous levodopa plus entacapone treatment, which included one night-time dose of controlled-release levodopa/carbidopa with entacapone. Forty-five patients were included in the PP population.

A total of 86% of all the levodopa doses used by patients at baseline were directly replaceable with Stalevo tablets containing the same amount (mg) of levodopa present in the standard-release formulation. In 60% of patients, all the levodopa doses used at baseline were directly replaceable with Stalevo tablets containing the same amount of levodopa. The most commonly used Stalevo strength was Stalevo 100 (81%, $n = 38$). A total of 40% ($n = 19$) used Stalevo 150 and 15% ($n = 7$) Stalevo 50. The majority of patients also rated the study treatment more favourably than their previous treatment (Table 3), i.e. more simple to dose (94%), more convenient to use (84%), easier to handle (84%), easier to remember (67%) and easier to swallow (59%).

The majority of patients preferred Stalevo to their previous levodopa/DDCI treatment, regardless of the DDCI used (carbidopa or benserazide). In the ITT population, the majority of patients (54%, $P = 0.162$) preferred Stalevo compared with 31% who preferred their prior treatment regimen. Fifteen per cent of patients preferred both treatments equally. Of patients taking one dose of controlled-release levodopa at night, 73% ($n = 11$) expressed a preference for Stalevo.

Stalevo treatment was predefined as successful if the patients' clinical condition was similar or better after treatment with Stalevo compared with their previous treatment. Stalevo was assessed to meet this criterion in 85% of patients, as rated by the investigator, and in 75% of patients, as rated by the patient.

**Table 3** Patient preference for treatment ($n = 49$)

| Characteristic | Study treatment | No preference | Previous treatment |
|---|---|---|---|
| Easier to handle | 41 (84) | 6 (12) | 2 (4) |
| Easier to remember | 33 (67) | 12 (24) | 4 (8) |
| Easier to swallow | 29 (59) | 14 (29) | 6 (12) |
| More simple to dose | 46 (94) | 1 (2) | 2 (4) |
| More convenient to use | 41 (84) | 4 (8) | 4 (8) |

Values are expressed as *n* (%).

The mean UPDRS score for parts I–III was improved from $35.6 \pm 13.4$ at baseline by $2.5 \pm 6.0$ points at the end of the study period (Week 4) ($P < 0.01$); and part III (motor score) was improved from $24.0 \pm 10.3$ by $1.9 \pm 4.9$ ($P < 0.01$) on Stalevo treatment.

The mean daily levodopa dose was lower at the end of treatment with Stalevo ($479 \pm 162$ mg), compared with $509 \pm 189$ mg during the control phase (a reduction of $24.6 \pm 50.9$ mg following Stalevo treatment). In 74% of patients the number of daily doses remained similar to that during the control period, while 21% of patients were able to decrease the number of doses by one per day. Only 19% of patients used levodopa booster doses while taking Stalevo, compared with 33% of patients using their usual regimen during the control phase.

There was no difference in the VAS measuring the quality of life between the two periods.

The switch from levodopa/DDCI and entacapone to Stalevo was well tolerated in the majority of patients, with treatment-emergent AEs reported by a total of 17 patients (Table 4). All AEs were considered as mild-to-moderate in severity. Three patients discontinued study treatment due to an AE, one for agitation, one for cervical dystonia and one for diarrhoea. Gastrointestinal and nervous system disorders were the most commonly reported AEs.

Only one serious AE was reported (dyspnoea, dizziness). The causal relationship of Stalevo to the event was assessed as unlikely by the investigator, and the patient continued in the study until

**Table 4** Adverse events during study treatment ($n = 52$)

| Adverse event* | Patients, *n* (%) |
|---|---|
| Dyskinesia | 2 (4) |
| Diarrhoea | 2 (4) |
| Nausea | 2 (4) |
| Upper respiratory tract infection | 2 (4) |
| Saliva increased | 1 (2) |
| Syncope | 1 (2) |
| Dizziness | 1 (2) |
| Dyspnoea | 1 (2) |
| Dystonia | 1 (2) |
| Headache | 1 (2) |
| Flatulence | 1 (2) |
| Back pain | 1 (2) |
| Agitation | 1 (2) |
| Somnolence | 1 (2) |
| Infection | 1 (2) |
| Bronchitis | 1 (2) |
| Inflicted injury | 1 (2) |
| Surgical intervention | 1 (2) |
| Rash | 1 (2) |
| Sweat discoloration | 1 (2) |

*WHO-ART preferred terms.

completion. There were no clinically significant findings in blood pressure or heart rate values during the study.

## Discussion

The results from this study show that most patients currently being treated with levodopa/DCCI plus entacapone for PD can be easily and successfully switched to Stalevo. To provide more insight into treatment preference, the results from a patient case study is discussed hereunder. This case study was compiled during the study.

In line with the findings of the pivotal phase III entacapone clinical trials, which revealed that the three available Stalevo dose combinations represent around 80% of individual levodopa dose combinations (17), 86% of all the levodopa doses used at baseline were directly replaceable with Stalevo. Treatment convenience was established in this study, as patients rated Stalevo as easier to remember, easier to handle, more simple to dose, easier to swallow and more convenient than their previous treatment. In addition, the majority of patients in the study preferred to continue with Stalevo rather than their previous treatment, although this preference was not statistically significant. Interestingly, 31% of patients stated that they would prefer to continue with their previous treatment, despite many of them rating Stalevo more highly in its characteristics and 15% of patients considered the two treatments to be equal. Given that, on average, the patients had been successfully treated with levodopa plus entacapone for 2 years prior to this study, it is possible that some patients may have preferred to stay on their previous treatment due to a reluctance to interfere with their current efficacious therapy. Moreover, at the time of the end of the study, Stalevo was not yet commercially available in Finland, which could explain some patient's preference for their previous treatment with levodopa plus entacapone.

Due to the bioequivalence of treatment schedules in relation to levodopa availability, no significant differences were anticipated in the clinical efficacy with Stalevo compared with the previous treatment. However, the UPDRS total score (parts I–III) as well as UPDRS motor score (part III) were reduced significantly ($P < 0.01$) on Stalevo, suggesting improvement in clinical disability in these patients. These responses were observed despite slightly lower daily levodopa doses with Stalevo than at baseline with the separate tablets. One possible explanation for this surprising result could be improved treatment compliance when entacapone is administered in the same tablet with levodopa/carbidopa. The combination of the three components in one tablet might prohibit forgetting, deliberate omitting, or dividing in half some doses of entacapone, as well as ensuring synchronous timing of ingestion of both enzyme inhibitors with levodopa.

A recent study of antiparkinsonian medication adherence in the UK found that 20% of PD patients do not take all of their medications and that this poor compliance was significantly associated with higher pill burden (19). As many patients with PD have complex dosing regimens for their medication, the simplicity of combining levodopa, a DDCI and entacapone in a single tablet has clear benefits in terms of ease of dosing and convenience. Indeed, these characteristics were rated as better in Stalevo compared with previous treatments by over 80% of patients in the study. For example, the previous antiparkinsonian medication regimen of the patient in the case study was particularly complex. The patient was receiving 900 mg of levodopa a day in the form of standard-release levodopa/carbidopa 100/25, six times a day; dispersible levodopa/benserazide 100/25, 0.5 tablets four times a day; and 0.5 tablets of controlled-release levodopa/carbidopa 200/50 once a day. Therefore, during the course of a day, the patient was taking a total of 11 levodopa and six entacapone tablets for his PD. During the study period the number of required tablets was reduced by over 60% to just six tablets a day. The patient was initially switched to Stalevo 100, four times a day, plus Stalevo 150, twice a day (total levodopa dose 700 mg). During the first 3 days of the study period, the patient developed dyskinesia and head and neck pain, which was thought to be possibly due to the study treatment. The levodopa dose was therefore reduced to 650 mg. The dyskinesia was not resolved but both the patient and the investigator rated Stalevo as better than the previous treatment in terms of treatment success. In addition, the patient rated Stalevo as superior to his previous treatment in all characteristics, and preferred to continue with Stalevo rather than his previous treatment. Interestingly, as this patient was previously receiving both carbidopa and benserazide, it is apparent that the switch from benserazide to carbidopa may be well tolerated and easily managed.

Overall, the switch to Stalevo was particularly straightforward for patients taking standard-release levodopa formulations, with 86% of these patients being able to replace their entire regimen without having to change the amount of levodopa taken. However, in 40% of patients all the levodopa doses at baseline were not directly replaceable

with Stalevo tablets and some dose adjustments were needed. The most common reason for dose adjustment was the use of controlled-release levodopa dose at baseline; 76% of subjects (16 of 21 subjects) who needed dose adjustment used controlled-release levodopa formulations. Nevertheless, 73% ($n = 11$) expressed preference for Stalevo, indicating that the switch from controlled-release levodopa to Stalevo is easily managed despite the fact that the levodopa dose may need to be altered. Therefore, the study demonstrates that the three available Stalevo dose combinations can easily replace patients' usual levodopa dosing regimens, regardless of whether they were using standard formulations alone or in combination with a bed-time controlled-release formulation.

Stalevo was well tolerated, with a low incidence of AEs. All AEs were considered to be mild to moderate in severity, and only three patients (5.7%) discontinued the study treatment due to an AE.

In summary, Stalevo is a safe and effective means of delivering levodopa, carbidopa and entacapone in one easy-to-use tablet that was preferred by the majority of patients to taking levodopa/DDCI and entacapone separately. Importantly, making the switch to Stalevo was easily managed by the clinician and well tolerated by the patient. An additional benefit was the significantly greater clinical efficacy shown by the mean UPDRS total and motor scores with Stalevo compared with the previous treatment at baseline, which may be as a result of better patient compliance.

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