APPENDIX 1. MANUSCRIPT

Efficacy and safety of Stalevo® in direct switch study in levodopa/DDCI treated Parkinson's disease patients with early wearing-off symptoms

ABSTRACT

Objectives

The aim of this study was to provide efficacy data of the direct switch from levodopa/carbidopa or levodopa/benserazide to levodopa/carbidopa/entacapone (Stalevo®) by clinical global impression of change (CGI-C) and to study the change in patient's clinical condition by change of Unified Parkinson's Disease Rating Scale (UPDRS) II (activity of daily living) and UPDRS III (motor disability). In addition, the quality of life (QoL) at baseline and the change from baseline at the end of the study by a QoL visual analogue scale (VAS) and the effect of Stalevo® on motor and non-motor wearing-off (WO) symptoms were studied.

Methods

This was a multicentre, multinational, open, single-group, non-randomised phase IV study which comprised a screening period and a 6-week treatment period. Altogether 115 Parkinson's disease (PD) patients with at least 1 wearing-off symptom (motor or non-motor) identified by using Wearing-Off Questionnaire with 9 questions

(WOQ-9) screening tool and treated with 3-4 doses of standard-release levodopa/dopa decarboxylase inhibitor (DDCI) (benserazide or carbidopa) switched directly to an equivalent dose of Stalevo®. The patients were stratified according to their previous DDCI use (benserazide or carbidopa).

The primary efficacy variable was switch-related efficacy from baseline assessed by the patient's CGI-C.

Investigator-assessed CGI-C, UPDRS parts II and III, quality of life VAS and effect of Stalevo® on symptoms of WO identified by the WOQ-9 at screening were secondary variables.

Results

PD patients with WO symptoms had significant benefit from Stalevo® regardless of previous DDCI treatment when assessed with CGI-C by patient and the investigator. There was also a significant improvement in UPDRS part II and III scores as well as in quality of life VAS scores during the 6 weeks study period. WOQ-9 was found to be useful in identifying patients with early WO-symptoms. Both motor and non-motor WO symptoms improved after switching to Stalevo®, although in general motor symptoms improved better than non-motor symptoms during this study.

Conclusions

Direct switch from levodopa/benserazide and levodopa/carbidopa to Stalevo® is safe and effective. WOQ-9 can be used to identify PD patients experiencing early WO symptoms who are likely to benefit from switch to Stalevo®.

Key Words: Parkinson's disease, Stalevo®, Wearing-Off

INTRODUCTION

Currently, the most effective and widely used treatment for PD is levodopa, which is invariably combined with a peripherally acting DDCIs carbidopa or benserazide. Nevertheless, despite co-administration with a DDCI, it is estimated that only about 10% of a levodopa dose reaches the brain (1, 2). Moreover, levodopa therapy is associated with a number of immediate and long-term drawbacks. The immediate drawbacks of levodopa include poor and variable gastrointestinal absorption, a short plasma half-life and competition for transport with dietary amino acids. The long-term drawbacks include a progressive shortening of efficacy, marked by fluctuations in clinical response, dose failures, dyskinesias, dystonias and psychiatric disturbances (3). Any strategy to improve the action of levodopa and prolong the effectiveness of this essential treatment is therefore of utmost importance to the patient.

Levodopa is metabolised by several enzymes, dopa decarboxylase (DDC) and catechol-O-methyltransferase (COMT) being the most important ones. COMT activity is high in peripheral tissues, such as liver, gut and kidney, where it metabolises levodopa to 3-O-methyldopa (3-OMD). Traditional levodopa/DDCI therapy shifts the peripheral metabolism of levodopa towards COMT, with O-methylation becoming the prominent metabolic pathway (1, 2). Optimising the traditional levodopa/DDCI therapy by dual enzyme inhibition, as is the case with Stalevo® (levodopa/carbidopa/entacapone), provides a further refinement in delivering

levodopa to the brain. Accordingly, phase III studies have demonstrated that levodopa/DDCI and entacapone therapy significantly decreases OFF-time in PD patients with wearing-off symptoms (4, 5). Potential further benefits of Stalevo® include better patient compliance and the possibility to decrease the number of daily tablets to be taken. The convenience and easy use of Stalevo® has also been recognised by the patients (6, 7).

Approximately 40% of PD patients experience wearing-off (WO) symptoms after 2 years of levodopa treatment (8). However, WO is probably under recognised especially in its early phases. To improve the identification of early WO, a specific screening tool, Wearing-Off Questionnaire with 9 symptoms (WOQ-9), has been developed (9, 10). The aim of this study was to find out whether the patients with at least 1 symptom identified by WOQ-9 will benefit from switching directly from levodopa/carbidopa or levodopa/benserazide to equivalent doses of Stalevo®. In addition, safety and tolerability data on the direct switch from levodopa/carbidopa or from levodopa/benserazide to Stalevo® was obtained.

MATERIALS AND METHODS

Study population

Male and female patients with diagnosis of idiopathic PD were included in the study. Patients were required to have at least one early wearing-off symptom (motor or non-motor) identified using a screening tool WOQ-9. All patients were required to have Hoehn and Yahr staging 1-3 during 'ON'-state. Eligible patients had been treated with 3-4 doses of standard-release levodopa/DDCI (maximum total daily dose of 600 mg of standard-release levodopa) and had unchanged antiparkinsonian medication for at least 6 weeks preceding baseline. One evening dose of controlled-release (CR) levodopa/DDCI and one dose of soluble levodopa/DDCI as the first morning dose were allowed. Patients with unpredictable OFF-periods or any peak-dose dyskinesia were excluded from the study.

Study design and treatments

This was a multicentre, multinational (patients enrolled in 25 centres in Germany, Sweden and the UK), open, single-group, non-randomised phase IV study performed in compliance with principles of Declaration of Helsinki of the World Medical Assembly and good clinical practice (ICH/135/95). The study protocol and any relevant amendments were reviewed and approved by the local Ethics Committees and national Competent Authorities.

The study comprised a screening period and a 6-week treatment period. A Screening visit took place within 2 weeks prior to the start of treatment period (baseline visit) and study visits at weeks 1, 2, 4 and 6 (end-of-study visit). A telephone contact was made on Day 3 or 4.

3 different strengths of Stalevo® tablets were used in the study:

Stalevo® 50: levodopa/carbidopa/entacapone 50/12.5/200 mg

Stalevo® 100: levodopa/carbidopa/entacapone 100/25/200 mg

Stalevo® 150: levodopa/carbidopa/entacapone 150/37.5/200 mg

The dosage was determined by the patient's previous standard levodopa/DDCI treatment (3-4- doses per day, maximum total daily dose 600 mg levodopa) which was switched to an equivalent dose of Stalevo® without changing the number of daily doses. The daily dose of levodopa could be adjusted according to patient's clinical response during weeks 1 and 2 where after the Stalevo® dosage was to be kept constant as far as possible. The number of doses was not to be changed during the study after the initial dose adjustment period.

Variables and assessments

The primary efficacy variable was switch-related efficacy from baseline assessed by the patient's CGI-C at 6 weeks/premature discontinuation.

Secondary efficacy variables were change in the patient's clinical condition from baseline by investigator-assessed CGI-C at 6 weeks or at premature discontinuation; the UPDRS parts II and III assessed preferably after the second or third daily study treatment dose (could be assessed already after the first daily dose) at the same time during each visit 2-3 hours after the previous study treatment dose (at baseline, weeks 2, 4 and 6 or at premature discontinuation); the health related quality of life assessed at baseline and at week 6 or at premature discontinuation using 100 mm visual analogue scale (VAS); and the effect of Stalevo® on symptoms of WO identified by the WOQ-9 at screening assessed at week 6 or at premature discontinuation.

In addition daily levodopa dose (mg) and the scheduled study treatment dose were recorded at baseline and changes in the study treatment were recorded at every visit and during the telephone contact

Safety

Vital signs were recorded during each visit. Physical examination was performed at screening visit and at end-of-study visit (week 6). Patients' body weight was measured at screening visit and at end-of-study visit. A standard 12-lead electrocardiogram (ECG) was recorded at screening visit in a supine position. Adverse events (AEs) were assessed throughout the study and classified according to Medicinal Dictionary for Regulatory Activities (MedDRA). Laboratory safety tests (haematology, clinical

chemistry, pregnancy test for females of childbearing potential) were performed at screening visit and at end-of-study visit.

Statistical analysis

For the CGI-C scores the success rate was defined as the percentage of patients with the outcome ‘improvement’ (a little improved, much improved, very much improved). The treatment success rate was analysed by calculating a p-value comparing the success rate to a threshold of 50% using binomial distribution.

Sum of the scores of the UPDRS Parts II and III were compared to the scores obtained at baseline. Statistical analysis included covariates centre, visit, DDCI group and interaction between visit and DDCI group. Furthermore, the difference between the DDCI groups was estimated. All the WO symptoms present at screening and the changes in these symptoms were reported by frequency tabulations. VAS scores assessed at baseline and at end-of-study visit were reported. The change from baseline was calculated and reported descriptively.

RESULTS

Study population

A total of 130 PD patients were screened and 115 patients (44 females and 71 males) were entered into the study and stratified according to the previous DDCI so that 68 used benserazide and 47 carbidopa combinations. Two patients were excluded from the intention-to-treat (ITT) population due to lack of post-baseline efficacy measurements. Patient characteristics at baseline are presented in Table 1.

At screening all patients had at least one motor WO symptom identified by WOQ-9 at screening. 82.3% of the patients had in addition at least 1 non-motor symptom.
WO symptoms at screening are summarised in Figures 1 and 2.
107 patients completed the study. 7% (8/115) of patients discontinued the study after randomisation. 5 patients discontinued due to AE, 1 patient due to lack of efficacy, 1 patient due to withdrawal of consent, and 1 patient's physician had stopped the treatment. All patients gave their informed consent before enrolment to the study.

Efficacy results

At week 6, 77% of patients showed improvement ($p < 0.0001$) as evaluated using the patient-assessed CGI-C (82.1% of patients in benserazide group [$p < 0.0001$] and 69.6% in carbidopa group [$p = 0.008$]). In investigator-assessed CGI-C, 84.1% of the

patients showed improvement ($p < 0.0001$) (86.6% of patients in benserazide group [$p < 0.0001$] and 80.4% in carbidopa group [$p < 0.0001$]) (Figure 3).

UPDRS scores (part II, III and II + III combined) improved from baseline in both groups significantly ($p < 0.01$). Mean (± SD) change from baseline at week 6 for the whole study population (ITT-Last-observation carried forward, LOCF) was -2.8 (2.8), -7.4 (6.5) and -10.2 (8.4) for UPDRS part II, III and II + III, respectively. The mean (± SD) changes from baseline at week 6 for the UPRDS II, III, II + III by DDCI group were comparable in both DDCI groups, i.e. -3.2 (2.5) vs. -2.1 (3.1), -7.4 (6.0) vs. -7.4 (7.3) and -10.7 (7.8) vs. -9.6 (9.3) for benserazide vs. carbidopa, respectively.

Quality of life VAS scores improved in both DDCI groups, mean change from baseline being 4.5 ± 16.3 (3.4 ± 13.4 in benserazide group and 6.0 ± 19.9 in carbidopa group).

At 6 weeks motor WO symptoms present at screening had improved in 62% of patients (65.4% in benserazide group and 57.2% in carbidopa group). In 30.6% of patients there were no change and in 7.4% of patients motor-symptoms had worsened. Non-motor symptoms had improved in 37.6% of patients (37.9% in benserazide group and 37.2% in carbidopa group). In 54.5% of patients there were no change and in 7.9% of patients non-motor-symptoms had worsened. Summary of

changes in WO symptoms that were present at screening is presented in Figures 4 and 5.

During the study period (6 weeks) 44 (38.9%) patients (40.3% in benserazide group and 37.0% in carbidopa group) had adjusted their daily levodopa dose or dosing frequency. Dosing frequency was maintained at baseline level in 94% of patients. Among those who adjusted the dose, the reasons for dose adjustment were AE (9 patients, 5 in benserazide group and 4 in carbidopa group), lack of efficacy (35 patients, 20 in benserazide group and 15 in carbidopa group) or other reason (7 patients, 5 in benserazide group and 2 in carbidopa group).

Safety

AEs were experienced by 68.7% of the patients (61.8% in benserazide group and 78.7% in carbidopa group). The most common AEs (> 5% in the patients) were chromaturia, nausea, diarrhoea, vertigo and dyskinesia. AEs are presented in Table 2.

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72.3% of the AEs were considered mild, 25.9% moderate and 1.8% severe. Severe AEs were vomiting, freezing phenomenon and tremor.

4 serious adverse events (SAEs) were experienced during the study by 3 patients (2.6%). One subject experienced 2 SAEs, skin infection and pacemaker complication, 1 patient had upper respiratory tract infection and 1 patient experienced hallucination.

There was no significant difference in AEs between patients whose previous DDCI treatment was benserazide or carbidopa.

There were no significant changes in ECG, vital signs or laboratory values during the study.

DISCUSSION

Currently, the most effective and widely used treatment for PD is levodopa, which is invariably combined with a peripherally acting DDCIs carbidopa or benserazide. This treatment can be further optimised by dual enzyme inhibition (i.e. Stalevo® levodopa/carbidopa/entacapone), providing further improvement in the delivery of levodopa to the brain. Previous studies have demonstrated that this approach leads to increased bioavailability of levodopa (11, 12) resulting in improved symptom control in PD patients with more advanced disease and clear-cut motor fluctuations (4, 5).

The patients in this study were on 3-4 daily doses of levodopa/carbidopa or levodopa/benserazide and they were screened to have at least one symptom of WO using the recently developed WOQ-9 (10). All the patients included into the study had at least one motor WO symptom and about 80% of them had in addition at least one non-motor WO symptom. The frequency of different motor WO symptoms listed in WOQ-9 ranged from 53% (muscle cramping) to 91% (any slowness of movement). In turn, the frequency of different non-motor WO symptoms listed varied between 20% (anxiety/panic attacks) and 54% (cloudy mind/slowness of thinking). These baseline data demonstrate that non-motor symptoms are common during WO and that they should be kept in mind when dealing with WO related matters.

At baseline, the patients' treatment with levodopa/carbidopa or levodopa/benserazide was switched directly to equivalent doses of Stalevo®. Overall, about 80% of patients improved according to the measurements of CGI-C by the patient and the investigator demonstrating that switch to Stalevo® significantly improved symptom control in the patient population studied. Also quality of life VAS scores and UPDRS part II, III and II + III scores improved significantly after switching to Stalevo®. These results are in line with the previously published findings (6).

The treatment effect was also measured at the end of the 6-week follow-up by assessing those individual WO symptoms which were identified at baseline by WOQ-9. Overall, it turned out that the motor and non-motor WO symptoms present at baseline were improved after switching to Stalevo® in 62% and 38% of cases, respectively. Of the motor and non-motor symptoms, tremor (improved in 74% of cases) and mood changes (improved in 52% of cases) had the best response to Stalevo®.

In general, Stalevo® was well tolerated in this study. The most common AE during the study was chromaturia, which is a harmless phenomenon.
Other common AEs (> 5% in the patients) included nausea, diarrhoea, vertigo and dyskinesia. Dyskinesia developed in 6 (5.2%) patients during the study. It was interesting to note that, despite developing dyskinesia, 5 of these patients felt improvement (patient-assessed GCI-C) during the study. There were no significant

differences in AEs between patients switching to Stalevo® from their previous levodopa/benserazide or levodopa/carbidopa treatments. Most of the AEs were considered mild (72%) or moderate (26%) and no unexpected safety concerns were raised.

In summary, the present study demonstrated that WOQ-9 is an effective tool to identify PD patients experiencing early WO. In addition to motor symptoms, non-motor symptoms appeared to be relatively common. Both improved after switching to Stalevo®, although motor WO symptoms tended to respond better. It can be concluded that the direct switch from levodopa/benserazide and levodopa/carbidopa to Stalevo® was effective leading to significant symptom improvement as assessed by many subjective and objective variables. Treatment with Stalevo® was safe and well tolerated.

TABLES:

Table 1. Characteristics of patients at baseline

	Benserazide group	Carbidopa group
Male/female, %	63/37	60/40
Age, years	69.3 ± 8.9	71.3 ± 7.4
Time from PD diagnosis, years	5.4 ± 3.8	5.2 ± 4.2
Duration of levodopa treatment, years	4.3 ± 3.8	4.1 ± 4.1
Daily levodopa dose, mg	331 ± 96	337 ± 83
Number of levodopa doses/day		
3, %	60.3	48.9
4, %	39.7	51.1
Other antiparkinsonian medication, %	64.7	76.6

Table 2. Adverse events

	Benserazide group	Carbidopa group	Total
Chromaturia	8 (11.8)	15 (31.9)	23 (20.0)
Nausea	7 (10.3)	6 (12.8)	13 (11.3)
Diarrhoea	4 (5.9)	2 (4.3)	6 (5.2)
Dyskinesia	4 (5.9)	2 (4.3)	6 (5.2)
Vertigo	2 (2.9)	4 (8.5)	6 (5.2)

FIGURES:

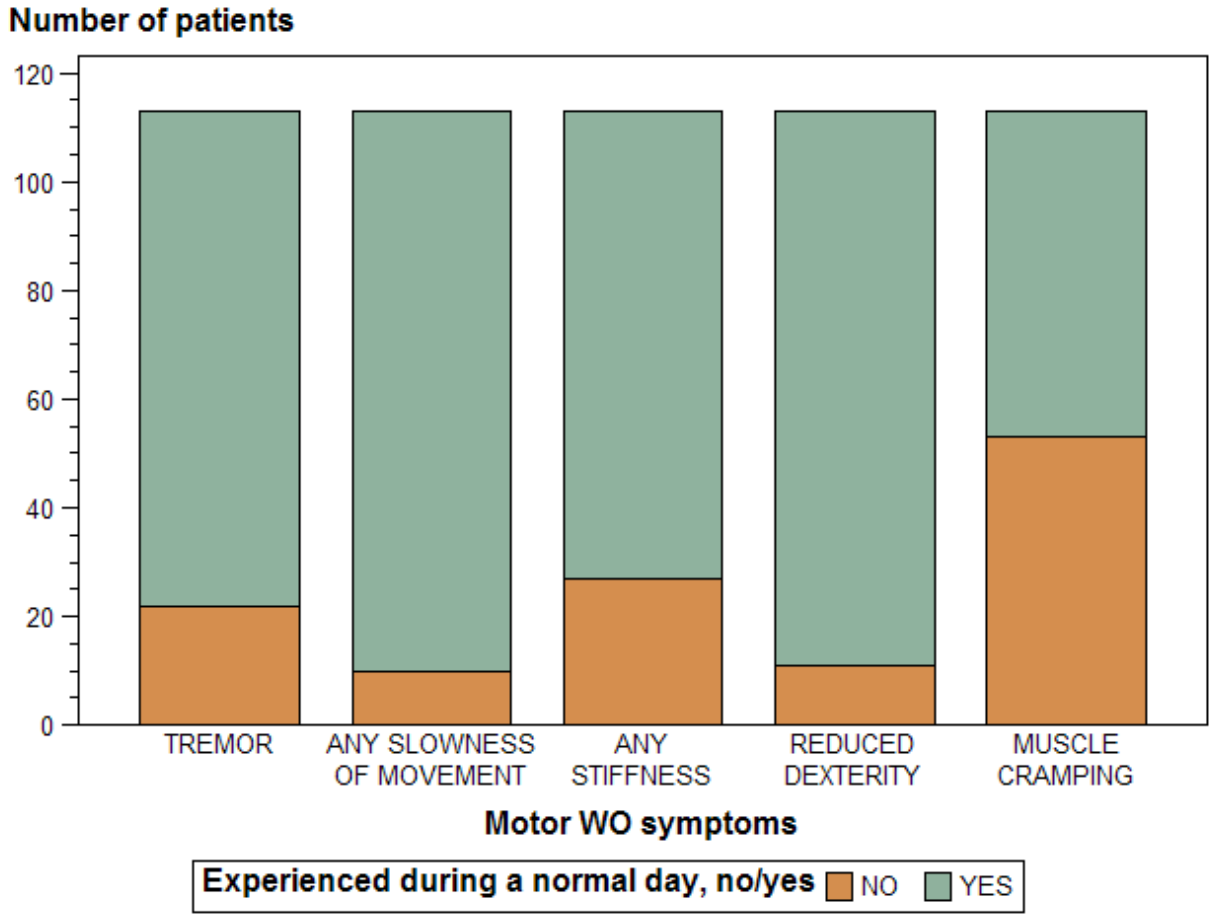

Figure 1. Number of patients with motor wearing-off symptoms at screening

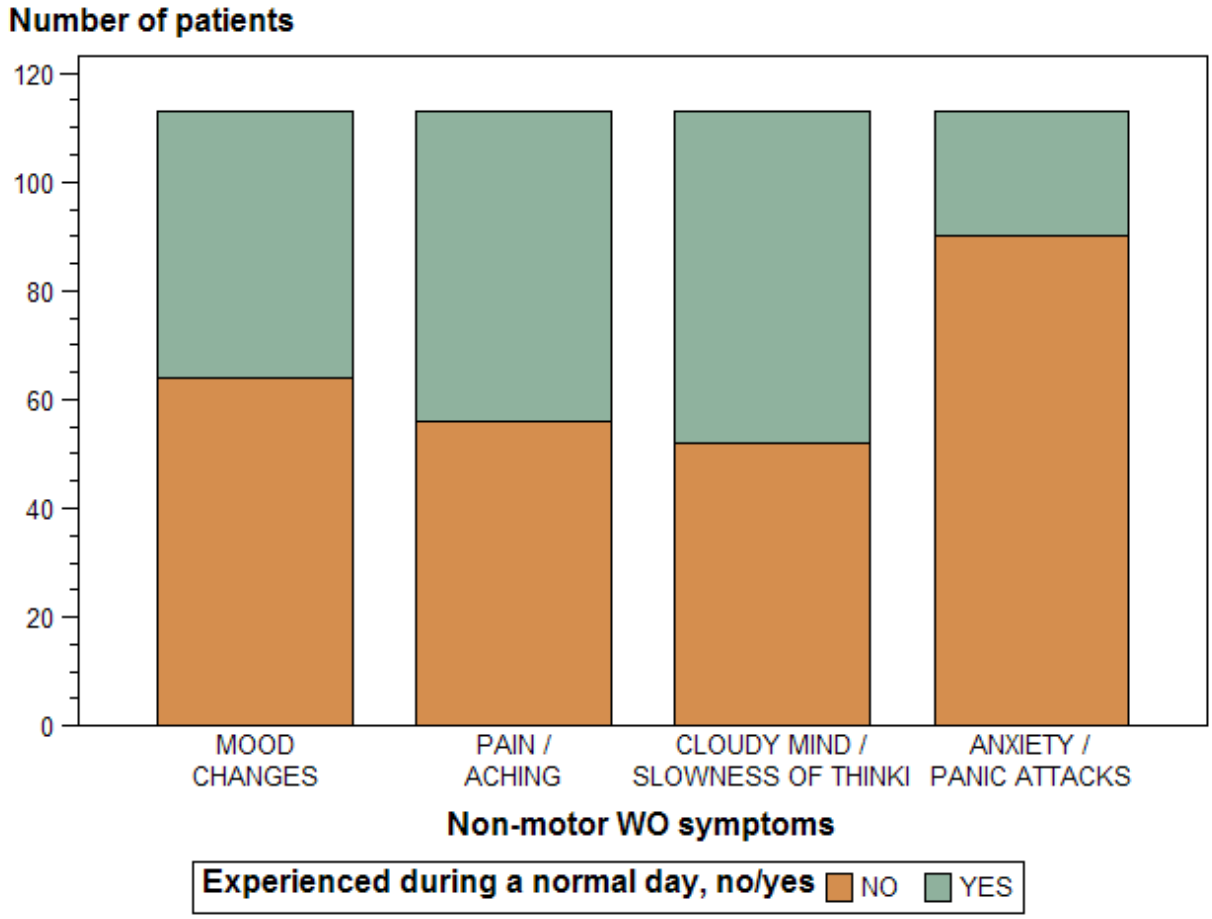

Figure 2. Number of patients with non-motor wearing-off symptoms at screening

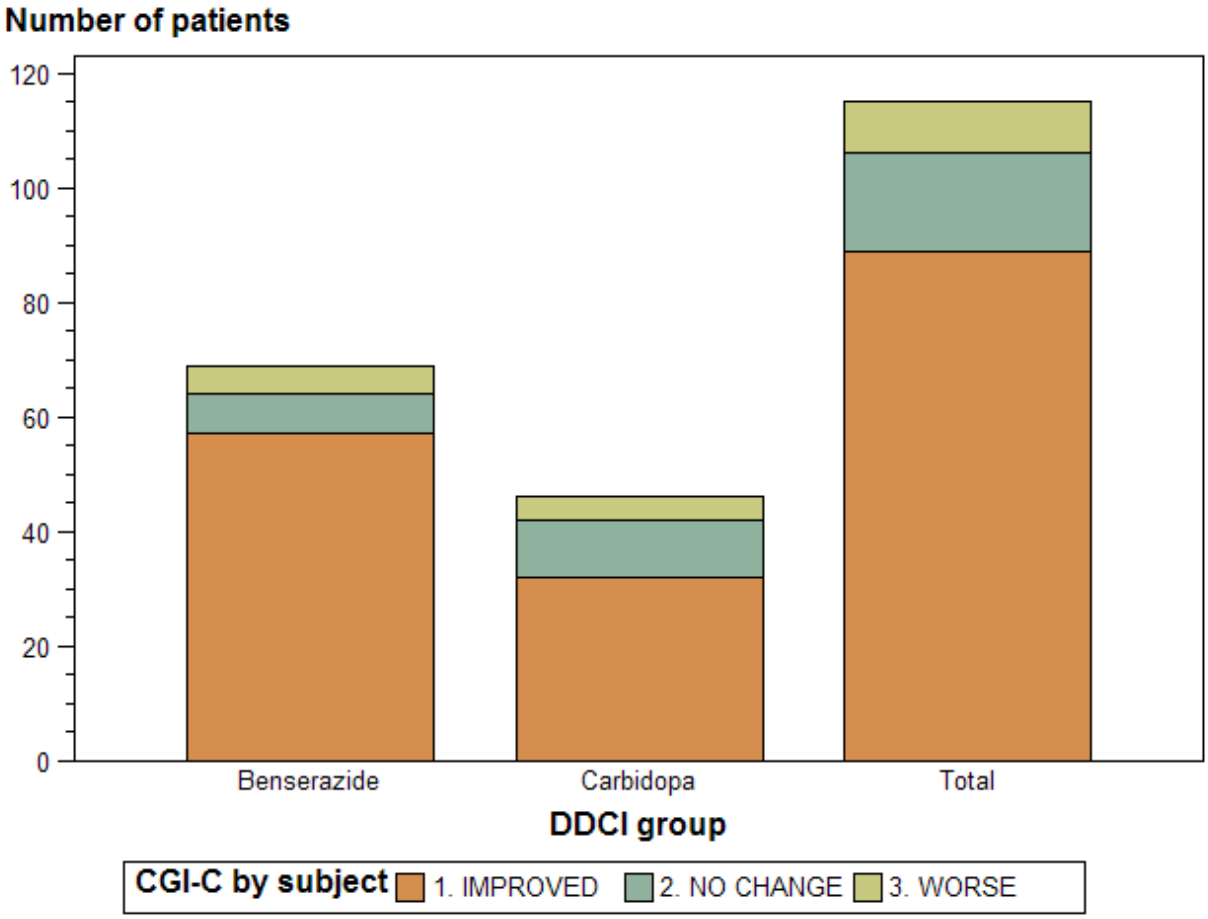

Figure 3. Patient assessed-CGI-C at week 6 ($p < 0.01$)

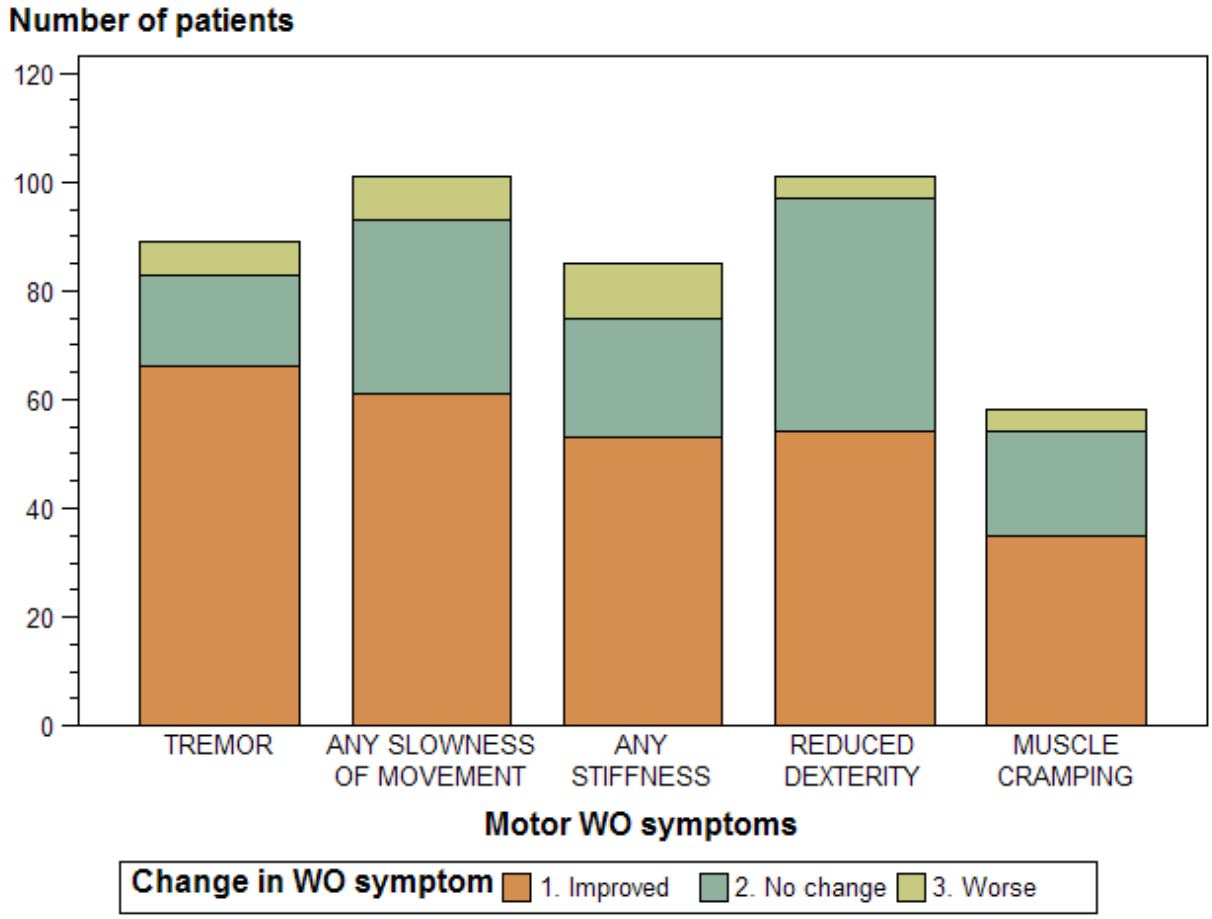

Figure 4. Changes in motor WO symptoms present at screening

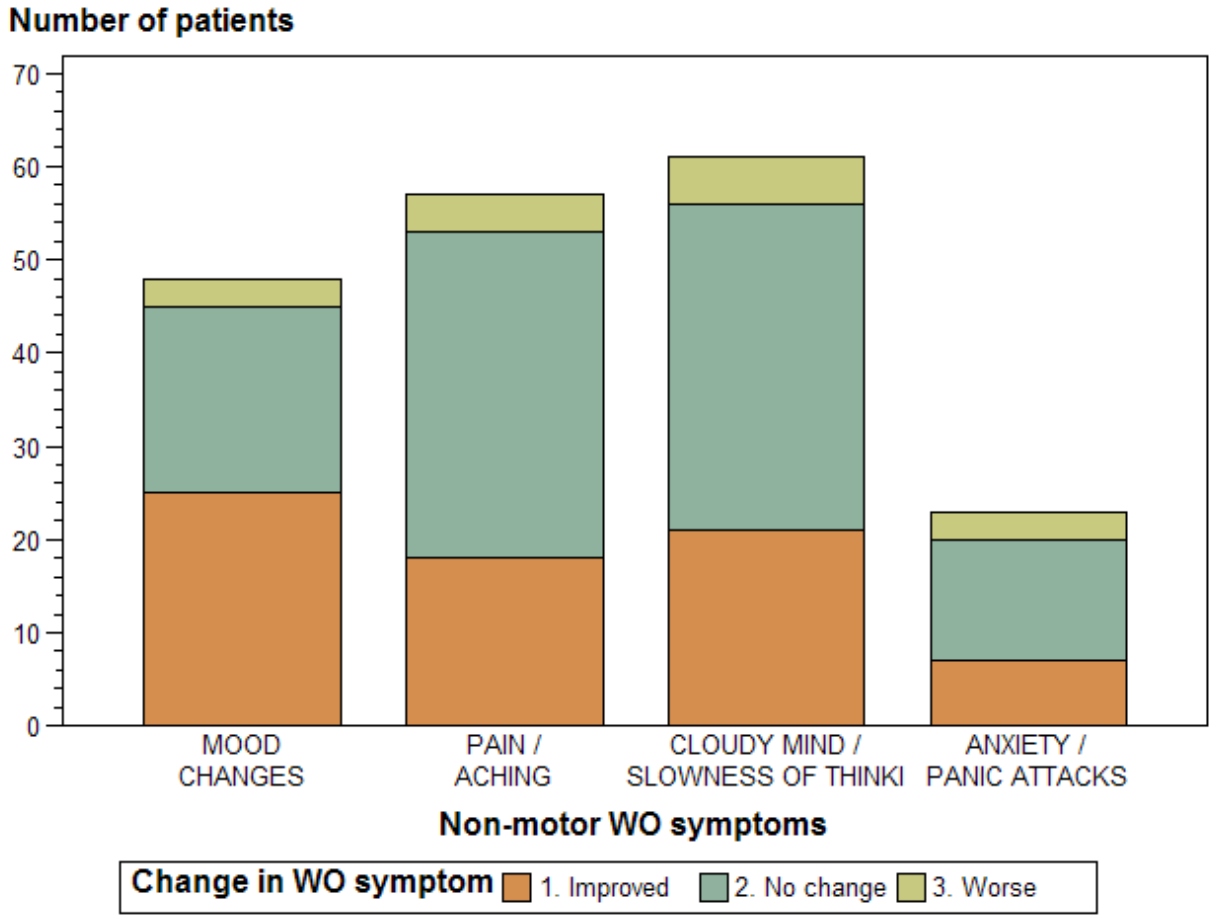

Figure 5. Changes in non-motor WO symptoms present at screening

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