

## 1.0 Abstract

### Title

Study On Patient- And Caregiver-Reported Symptoms And Outcomes With Levodopa/Carbidopa Intestinal Gel For The Treatment Of Advanced Parkinson's Disease.

ADEQUA Study.

### Keywords

Levodopa/carbidopa intestinal gel, Quality of life, Well-being, Advanced Parkinson's disease, Caregivers.

### Rationale and Background

LCIG has demonstrated benefits controlling motor fluctuations and non-motor symptoms. However, little evidence is available on the effects of LCIG on quality of life, mood and behavior.

Patient reported outcomes (PRO) has become an important endpoint to be assessed in clinical trials. Among these, the assessment of perceived symptoms is particularly relevant since the adequate management of symptoms and medication side effects has been demonstrated to be crucial to treatment success. It is important to understand the relationship between medication and patients' symptomatology, quality of life and wellbeing.

We predicted that LCIG would significantly improve quality of life and this improvement will be related to improvements in motor symptoms, non-motor symptoms and mood and behavior symptoms, compared to baseline in patients with advanced Parkinson's disease not well controlled with conventional treatment.

### Research Question and Objectives

The primary objective of this post-marketing observational study (PMOS) was to assess the effect of LCIG treatment on the quality of life of patients with advanced

Parkinson's disease, between baseline and 6 months after discharge from hospital, using the Parkinson's Disease Questionnaire (PDQ-39).

Additionally, the study had five secondary objectives: (i) to assess motor and non-motor symptoms of the patients using the Unified Parkinson's Disease Rating Scale-III (UPDRS-III) and the Non-Motor Symptoms Scale (NMSS), respectively; (ii) to assess the emotional well-being, fatigue, apathy, depression, anxiety, and treatment satisfaction of the patients using the Norris/Bond-Lader visual analog scale, the Parkinson's Disease Fatigue Scale (PFS), the Starkstein Apathy Scale (AS), the Beck Depression Inventory second edition (BDI-II), the Beck Anxiety Inventory (BAI), and the Treatment Satisfaction with Medicines Questionnaire (SATMED-Q), respectively; (iii) to assess the quality of life, anxiety and depression, burden of the disease, and work productivity of the caregivers using the Scale of Quality of Life of Care-Givers (SQCL), the Goldberg Anxiety and Depression scale (GADS), the Zarit Burden Interview (ZBI) and the Work Productivity and Activity Impairment questionnaire (WPAI), respectively; (iv) to assess the correlation between quality of life with motor, non-motor symptoms and emotional well-being, for both patients and caregivers, and (v) to assess the correlation between patient and caregiver scores on quality of life, motor and non-motor symptoms and burden of the disease.

### **Study Design**

Post-marketing observational study (PMOS) multicenter, national.

### **Setting**

In this PMOS, LCIG was prescribed in the usual manner, in accordance with the terms of the local marketing authorization. The decision of prescribing LCIG was independent of the patients' participation in this study. Information about principal caregiver was collected when possible. Principal caregiver was the person in charge of the care of the patient most of the day-time.

## **Subjects and Study Size, Including Dropouts**

In this study, 62 patients from 24 Spanish centers were enrolled. 59 out of 62 patients were evaluable and three were non-evaluable because they did not participate in the nasoduodenal test phase and they did not receive any dose of levodopa/carbidopa intestinal infusion gel. These 59 patients constituted the Intent-To-Treat and Safety populations. 6 (10.17%) out of these 59 patients prematurely discontinued the study, 3 during the nasoduodenal test phase (due to lack of efficacy in 2 cases, and due to a very narrow therapeutic margin in 1 case); and 3 after the percutaneous endoscopic gastrostomy intervention phase (in 1 case due to lack of efficacy, due to exitus in other case, and due to patient's decision in the third case). In addition, 1 patient did not fulfill the PDQ-39 questionnaire at the end of the treatment. Thus, 52 patients constituted the Per Protocol population.

## **Variables and Data Sources**

For patients:

- Socio-demographic and Clinical variables: through patient's medical records
- Quality of Life: Parkinson's Disease Questionnaire (PDQ-39)
- Motor and non-motor symptoms: Unified Parkinson's Disease Rating Scale-III (UPDRS-III) and Non-Motor Symptoms Scale (NMSS)
- Treatment satisfaction: Treatment Satisfaction with Medicines Questionnaire (SATMED-Q)
- Mood: Norris/Bond-Lader VAS
- Fatigue: Parkinson's Disease Fatigue Scale (PFS)
- Apathy: Starkstein Apathy Scale (AS)
- Depression and Anxiety: Beck Depression Inventory second edition (BDI-II) and Beck Anxiety Inventory (BAI)

For primary caregivers:

- Socio-demographic: Questionnaire
- Quality of Life for caregivers: Scale of Quality of Life of Care-Givers (SQCL)
- Burden of the disease for caregivers: Zarit Burden Interview (ZBI)

- Depression and Anxiety for caregivers: Goldberg Anxiety and Depression scale (GADS)
- Work productivity: Work Productivity and Activity Impairment questionnaire (WPAI)

Other variables not related to primary or secondary objectives were collected. See sections 9.4 and 9.5.

## Results

Intent to treat (ITT), per protocol (PP), and safety (SP) populations are defined in section 10.1. Due to definition of ITT and PP populations, differences per patient between final and baseline could be missing, so descriptives and tests over means and medians on ITT and PP analysis for some questionnaires could be similar, even identical. As no differences were found between results obtained in ITT and PP populations, in this abstract only results for ITT population are described.

Socio-demographic characteristics of the patients and caregivers and clinical characteristics of the patients are detailed in sections 10.2.1 and 10.2.2.

Patients showed a statistically significant improvement in their QoL from baseline to visit 4 (after 6 months). The mean PDQ-39 score changed from  $46.71 \pm 13.59$  at baseline to  $33.66 \pm 16.87$  at visit 4, ( $p < 0.0001$ ). Changes were also statistically significant in all PDQ-39 domains except in the domain “Social support”.

The mean UPDRS-III score, assessed in ON state, changed from  $30.08 \pm 14.17$  at baseline to  $22.89 \pm 11.59$  at visit 4 ( $p = 0.0002$ ). Changes were statistically significant in NMSS total score and in all NMSS domains.

Patients showed a statistically significant positive change in mood. The Norris/Bond-Lader mean global score changed from  $42.62 \pm 17.57$  at baseline to  $36.57 \pm 16.57$  at visit 4 ( $p = 0.0297$ ). When the Norris/Bond-Lader factors were analyzed, the improvements were only statistically significant in the Alertness/sedation and Calmness/relaxation factors, with mean scores changing from  $44.76 \pm 19.66$  at baseline to  $37.70 \pm 17.28$  at visit 4 ( $p = 0.0279$ ) and from  $53.90 \pm 23.25$  at baseline to

45.25 ± 23.64 at visit 4 (p= 0.0047), respectively. Patient's fatigue, depression, and anxiety showed a statistically significant improvement, too. From baseline to visit 4, mean PFS-16 score changed from 3.70 ± 0.77 to 3.11 ± 0.56 (p= 0.0003), mean BDI-II changed from 18.09 ± 9.75 to 13.19 ± 10.18 (p= 0.0002), and mean BAI changed from 19.84 ± 9.36 to 13.77 ± 10.13 (p< 0.0001). Nevertheless, there was a slight worsening, non-statistically significant, on patient's apathy with the mean AS score changing from 11.41 ± 6.40 at baseline to 12.34 ± 6.52 at visit 4 (p= 0.5877). Patients' satisfaction with the treatment showed a statistically significant improvement with a mean SATMED-Q score changing from 52.81 ± 15.75 at baseline to 68.87 ± 11.95 at visit 4 (p< 0.0001). When SATMED-Q was analyzed according its domains, a statistically significant improvement was seen in all of them, except in the Medical care and Global satisfaction domains.

Caregivers' quality of life showed a slight improvement but the change was not statistically significant. The mean SQLC score changed from 63.63 ± 26.45 at baseline to 66.10 ± 28.72 at visit 4 (p= 0.3126). Changes observed in all SQLC domains did not reach statistical significance neither. A slight improvement on caregiver's burden was observed, with the mean ZBI score changing from 24.91 ± 13.56 at baseline to 24.40 ± 14.28 at visit 4, but the change was of no statistical significance. The mean CSI score showed a non-statistically significant slight improvement, changing from 5.02 ± 3.33 at baseline to 4.46 ± 3.25 at visit 4 (p= 0.1945). Mean depression score showed a non-statistically significant worsening, changing from 5.68 ± 1.95 at baseline to 6.00 ± 1.41 at visit 4 (p= 0.7939). Nevertheless, a statistically significant improvement was observed when caregivers' anxiety was assessed, with the mean score changing from 7.18 ± 1.33 at baseline to 6.40 ± 1.24 (p= 0.0234). From baseline to visit 4, the percentage of work time missing was reduced from 12.00 ± 27.46 to 10.56 ± 14.05, the percentage of work impairment while working was reduced from 26.43 ± 28.18 to 15.45 ± 18.09, the percentage of overall work impairment was reduced from 36.06 ± 33.91 to 25.39 ± 21.79, and the percentage of activity impairment was reduced from 25.63 ± 25.29 to 24.00 ± 17.13. Nevertheless, the improvements did not reach statistical significance.

A statistically significant correlation was found between the quality of life of the patients and motor symptoms, patients' anxiety, patients' depression, patients' fatigue, Norris/Bond-Lader Contented/discontented factor, caregivers' burden and caregivers' depression. At the end of the study, a statistically significant correlation was observed between patients' quality of life and all the analyzed variables except patient's apathy and caregivers' depression.

At baseline, a statistically significant correlation was observed between caregivers' quality of life and caregivers' burden, caregivers' depression and patients' quality of life. At visit 4, a statistically significant correlation was observed between caregivers' quality of life and caregivers' burden and patients' quality of life.

A total of 18 serious adverse events (SAEs) were reported in 13 (22.03%) patients, the most common affecting the gastrointestinal tract (38.88% of all SAEs), followed by cardiac disorders (27.77%). Three out of the 18 SAEs were reported in the nasoduodenal phase; of them, only 1 was related to LCIG. Fifteen out of the 18 SAEs were reported in the post-PEG phase; of them, 7 were related to LCIG. One patient died due to a cervical vertebral fracture not related to the study drug

## **Discussion**

This post-marketing observational study carried out under standard clinical practice conditions has demonstrated that LCIG administration for 6 months has a positive impact in the quality of life of patients with advanced Parkinson's disease. This result is in agreement with those obtained in other observational [29,30,54,57-59,61,62] and interventional [27, 28, 64] studies. Only in one retrospective, open-label study LCIG treatment failed in showing a significant improvement in patient's quality of life [69]. Three main differences could explain the fact that the improvement seen in the study of Fasano et al. did not reach statistical significance; the number of patients (14 vs 59), the questionnaire used (PDQ-8 vs PDQ-39) and the months of followed-up (approximately 25 months vs 6 months). It is licit to think that the beneficial effect of the treatment can be mitigated by the progression of the disease. Nevertheless, the improvement in patients' quality of life have been observed even after 4 years of treatment with LCIG [63].

The efficacy of LCIG in the control of both motor and non-motor symptoms has been demonstrated in numerous clinical studies [27-33,54,55,57-63,64], and not surprisingly, in this study a significant reduction in UPDRS-III and NMSS scores, including all NMSS domains, has been observed, too.

One of the most distinctive features of the ADEQUA study is the assessment of LCIG impact on the emotional well-being of patients with advanced Parkinson's disease. Noticeably, patient's apathy showed a non-statistically worsening. Nevertheless, patients' mood, fatigue, anxiety and depression improved after six months of treatment with LCIG. At the end of the study, a correlation was seen between patients' quality of life and patients' motor and non-motor symptoms, and patient's anxiety, depression, fatigue, and mood. These findings are relevant, as depression [65,66] and anxiety [67,68] had already been identified as major contributors to poor quality of life. Thus, in order to improve the quality of life of patients with Parkinson's disease the administration of therapies that not only improve motor symptomatology but also contribute to reduce these neuropsychiatric symptoms are of great importance.

The global improvements in motor and non-motor symptoms obtained with the administration of LCIG can easily explain the improvement in the satisfaction of the patients with the study medication as assessed with the SATMED-Q questionnaire.

Interestingly, in the ADEQUA study, the clear benefit obtained with LCIG treatment in the control of the patients' symptomatology seems not to correlate with the effect that the treatment had in their caregivers, as only caregivers' anxiety was significantly reduced at the end of the study, and non-statistically significant improvements were seen in caregivers' quality of life, caregivers' burden, caregivers' stress, caregivers' depression and caregivers' productivity. In fact, when the factors that could impact the caregivers' quality of life were investigated, at the end of the study, a significant correlation was only seen between caregivers' quality of life and caregivers' burden, and patients' quality of life. These results are in disagreement with those published by Santos-García et al. [58] who found moderate to strong correlations between

caregivers' burden and caregivers' stress, and patient's motor and non-motor symptoms, patients' depression and patients' disability.

In conclusion, this study has demonstrated that LCIG administered during 6 months under routine clinical practice improves the quality of life of patients with advanced Parkinson's disease, as well as improves their motor, non-motor and emotional well-being. Nevertheless, no significant improvements were obtained in the quality of life of caregivers, caregivers' burden, caregivers' stress, caregivers' depression and caregivers' productivity; and only caregivers' anxiety was significantly reduced after 6-month treatment with LCIG.

Motor symptoms, non-motor symptoms and patients' emotional well-being (mood, fatigue, depression, and anxiety) contribute with the quality of life of patients with advanced Parkinson's disease. There is also a correlation between the caregivers' quality of life and the quality of life of the patients and the caregivers' burden.

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