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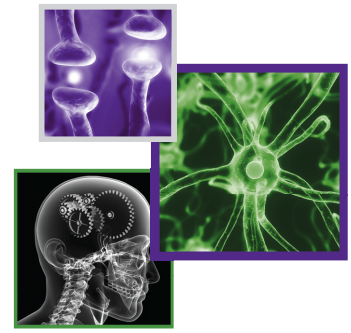

Age/disease duration influence on activities of daily living and quality of life after levodopa-carbidopa intestinal gel in Parkinson's disease

Angelo Antonini*,[1], Weining Z Robieson[2], Lars Bergmann[2], Ashley Yegin[2] & Werner Poewe[3]

[1]Department of Neuroscience, Padua University, Padua, 35122, Italy

[2]AbbVie, Inc., North Chicago, IL 60064, USA

[3]Department of Neurology, Medical University of Innsbruck, Innsbruck, A-6060, Austria

* Author for correspondence: Tel.: +39 041 220 7554; angelo3000@yahoo.com

Summary points

- Levodopa-carbidopa intestinal gel (LCIG) is delivered continuously via percutaneous endoscopic gastrojejunostomy to patients with advanced Parkinson's disease whose motor fluctuations are no longer sufficiently controlled by oral medication.
- GLORIA was a 24-month observational registry that evaluated long-term effectiveness of LCIG.
- This *post hoc* analysis assessed subgroups of patients by baseline age, disease duration, hours per day of 'off' time and levodopa equivalent dose (LED).
- Quality of life improvements were similar based on age and disease duration.
- Improvements in quality of life were greater in patients with more 'off' time and higher LED at baseline, suggesting that the magnitude of baseline disability may be a predictor of a clinical outcome.
- Improvements in activities of daily living appeared to be greater in patients treated with LCIG earlier in life, after shorter disease duration, and in those with the highest baseline LED.

Aim: To determine if age and Parkinson's disease duration at therapy initiation influence the efficacy of levodopa-carbidopa intestinal gel (LCIG) on quality of life and activities of daily living. **Patients & methods:** This *post hoc* analysis assessed subgroups of patients stratified by baseline age, disease duration, hours/day of 'off' time and levodopa equivalent dose. Patients' data were collected from the GLORIA study, a 24-month observational registry evaluating long-term effectiveness of LCIG. **Results & conclusion:** LCIG therapy led to sustained improvements in quality of life irrespective of patient age and disease duration at baseline. Improvements in activities of daily living were observed across all subgroups, particularly in younger patients, patients with shorter disease duration and in patients with the highest baseline levodopa equivalent dose.

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Keywords: activities of daily living • levodopa-carbidopa intestinal gel • quality of life

Levodopa is an effective treatment for troublesome motor symptoms associated with Parkinson's disease (PD). However, long-term use of oral levodopa is associated with the development of motor complications, including response fluctuations and potentially disabling dyskinesia [1–3]. The short half-life of levodopa and low [4] or irregular plasma bioavailability caused by erratic gastric emptying, as well as striatal pharmacodynamic changes are thought to play a role in the development of motor complications [5].

Levodopa-carbidopa intestinal gel (LCIG; also known as carbidopa-levodopa enteral suspension in the USA) is delivered continuously via percutaneous endoscopic gastrostomy with a jejunal extension tube (PEG-J) and is a treatment option for patients with advanced PD whose motor fluctuations are no longer sufficiently controlled by oral medication. Continuous delivery of LCIG to the upper intestine allows for more stable levodopa plasma levels when compared with oral levodopa [6]. LCIG is effective in reducing motor and nonmotor complications

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associated with oral levodopa therapy as well as improving quality of life (QoL) in patients with advanced PD, as demonstrated in both controlled [7–9] and open-label, routine-care settings [10–12].

Data from the Global Long-Term Registry on Efficacy and Safety of LCIG in Patients with Advanced Parkinson's Disease in Routine Care (GLORIA) registry were prospectively evaluated to determine the long-term effectiveness of LCIG [13,14]. LCIG was shown to improve motor and nonmotor symptoms as well as patient QoL and activities of daily living (ADL) [13,15]. Because some studies have reported reduced efficacy of therapies for advanced PD (deep brain stimulation and LCIG) in small sample sizes of patients with longer disease duration and advanced age [16,17], we assessed the contribution of age and PD duration on QoL and ADL in a large set of patients with advanced PD treated with LCIG.

Methods

Study design & treatment

GLORIA is a multinational (75 movement disorder centers in 18 countries), observational registry designed to collect efficacy and safety data of routine clinical care use of LCIG over 24 months via continuous LCIG infusion via PEG-J. The registry study was conducted in accord with the Good Clinical Practice Guidelines as defined by the International Council on Harmonisation, the Declaration of Helsinki, and/or all applicable national and local regulations and institutional review board requirements, as appropriate.

Clinical observations, including baseline observations, were collected prospectively for LCIG-naive patients. Enrolled patients received LCIG treatment with a temporary nasojejunal (NJ) tube to optimize dosing according to the existing label at the time the registry study was conducted. Following LCIG titration via NJ tube, patients were treated by continuous LCIG infusion via PEG-J for 24 months. Observations were partially retrospective and prospective for patients who enrolled in the study with a maximum of 12 months of LCIG treatment. Concomitant PD drugs were allowed at the discretion of the treating physician. Levodopa equivalent dose (LED) was calculated for LCIG and concomitant oral PD treatments for each study visit. LED was calculated from the reported administration of LCIG and all other PD treatments according to published conversion factors [18].

Patients

The GLORIA registry consisted of patients enrolled according to the European Summary of Product Characteristics (having advanced levodopa-responsive PD with severe motor fluctuations and hyper-/dyskinesia where available combinations of Parkinson medicinal products had not given satisfactory results) and national reimbursement criteria where applicable. Patients also had to be LCIG-naive or had to have received LCIG for a maximum of 12 months prior to enrollment. All patients provided written informed consent before enrollment in the registry.

Assessments

Efficacy assessment

Efficacy outcomes included the mean change from baseline to study visit in the Unified Parkinson's Disease Rating Scale (UPDRS) parts II, III and 'off' time and the dyskinesia items (items 32–34) from UPDRS part IV. UPDRS IV items 39 and 32 were modified using the rating instructions for the corresponding parts 4.3 and 4.1 of the Movement Disorder Society UPDRS to allow for collection of actual hours of 'off' time and 'on' time with dyskinesia. UPDRS was assessed in the 'on' state. Patient QoL was assessed via the eight-item Parkinson's Disease Questionnaire (PDQ-8). Efficacy was assessed at baseline before the initiation of LCIG via NJ tube; at discharge from hospital following PEG-J placement (day 1); and at 6, 12, 18 and 24 months after PEG-J placement.

Safety assessment

Adverse drug reactions included all adverse events that had a reasonable possibility of being related to the treatment drug or device (as determined by the investigator). Adverse drug reactions were recorded for the duration of the registry study and for 28 days after the patient's last visit.

Statistical analysis

All patients who received LCIG and had at least one post-baseline safety and efficacy evaluation were included. For this *post hoc* analysis, patients were allocated into groups based on the following baseline clinical characteristics: age (<65 years and ≥65 years), PD duration (<10 years and ≥10 years), hours per day of 'off' time based on UPDRS modified item 39 (<3, 3–6 and >6 h/day) and LED (<800, 800–1200 and >1200 mg/day). Disease

Table 1. Baseline demographics and characteristics: age and Parkinson's disease duration subgroups.

Patient demographics, n (%)	Age, years		PD duration, years	
	<65 (n = 122)	≥65 (n = 207)	<10 (n = 111)	≥10 (n = 217)
Sex				
– Male	79 (65)	118 (57)	71 (64)	125 (58)
– Female	43 (35)	89 (43)	40 (36)	92 (42)
Mean (SD) age, years	57.9 (5.7)	71.8 (4.4)	65.3 (8.9)	67.3 (8.0)
Race, white	116 (97)[†]	203 (99)[‡]	109 (98)	209 (99)[§]
Disease characteristics, mean (SD)				
PD duration, years	12.5 (7.1)	13.0 (5.8)	6.8 (2.2)	15.9 (5.4)
Baseline LED, mg/day	1419.8 (667.3)	1250.9 (562.2)	1305.9 (536.8)	1317.7 (643.7)
UPDRS part II: activities of daily living during 'on'	14.5 (10.3)	17.5 (9.3)	14.9 (9.6)	16.9 (9.9)
UPDRS part III: motor examination during 'on'	22.2 (11.1)	26.2 (12.3)	23.9 (11.4)	24.9 (12.3)
UPDRS part IV				
– Modified item 39: 'off' time, h/day	6.5 (3.2)	5.7 (3.1)	6.3 (3.4)	5.9 (3.0)
– Modified item 32: time with dyskinesia, h/day	4.9 (4.2)	3.8 (3.3)	3.6 (3.8)	4.6 (3.7)
PDQ-8 total score	44.4 (18.1)	48.3 (18.8)	45.6 (20.0)	47.3 (18.0)

[†]n = 120.
[‡]n = 204.
[§]n = 212.
LED: Levodopa equivalent dose; PD: Parkinson's disease; PDQ-8: Parkinson's Disease Questionnaire eight-item; SD: Standard deviation; UPDRS: Unified Parkinson's Disease Rating Scale.

duration was calculated as the time between PD diagnosis and enrollment in the registry. For each subgroup, the mean change from baseline to each time point was assessed for PDQ-8 score and UPDRS II score using a paired *t*-test. For patients with missing values, the last visit denotes the last observation carried forward. Last observation carried forward provides conservative estimates of within-group changes from baseline for this single-arm registry, thus avoiding overstating the LCIG treatment effect.

Results

Patients

Baseline demographics and disease characteristics were similar across all subgroups, although there were a few numerical differences within a subgroup (Tables 1 & 2). When compared with patients <65 years of age, older patients tended to have a lower baseline LED, a diminished ability to perform ADL (as indicated by higher UPDRS II scores), worse motor symptoms (as indicated by higher UDPRS III scores) and poorer QoL. Patients with a disease duration ≥10 years tended to have a diminished ability to perform ADL, and slightly worse motor symptoms and QoL compared with patients who had a disease duration <10 years. Within the 'off' time subgroup, patients with >6 h/day of 'off' time tended to be younger than patients who had a lower baseline 'off' time. Patients with >6 h/day of 'off' time also tended to have a higher baseline LED than patients who had <3 h/day of 'off' time; patients with <3 h of 'off' time had the lowest PDQ-8 scores, indicating highest QoL. Baseline characteristics were comparable across the three LED subgroups.

Efficacy

Age subgroups

Compared with baseline, LCIG treatment led to sustained and significant improvements in QoL through 24 months for patients in either age subgroup ($p < 0.05$ for all visits; Figure 1A); after 24 months of treatment, patients <65 years of age ($p = 0.03$) and those that were at least 65 years of age ($p < 0.001$) experienced a significant mean (standard deviation) reduction from baseline in PDQ-8 scores of 6.15 (21.9) and 7.69 (20.4), respectively. Significant improvements from baseline in ADL were observed in patients <65 years of age through month 18 ($p < 0.01$ for all visits up to month 18; Figure 1B). In contrast, patients aged ≥65 years experienced sustained significant improvements in ADL compared with baseline through month 6 ($p < 0.05$), but only a trend was observed between months 6 and 18.

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Table 2. Baseline demographics and characteristics: 'off' time and levodopa equivalent dose subgroups.

Patient demographics, n (%)	'Off' time, h/day			LED, mg/day		
	<3 (n = 28)	3–6 (n = 96)	>6 (n = 87)	<800 (n = 54)	800–1200 (n = 101)	>1200 (n = 172)
Sex						
– Male	14 (50)	57 (59)	49 (56)	25 (46)	49 (49)	123 (72)
– Female	14 (50)	39 (41)	38 (44)	29 (54)	52 (52)	49 (29)
Mean (SD) age, years	68.1 (8.0)	67.4 (7.7)	63.6 (8.9)	68.7 (8.4)	67.2 (8.4)	65.7 (8.2)
Race, white	27 (96)	96 (100)	84 (97)	53 (100)†	100 (99)	165 (98)‡
Disease characteristics, mean (SD)						
PD duration, years	12.1 (6.8)	12.8 (5.6)	12.8 (6.5)	12.8 (7.0)	12.6 (5.5)	12.9 (6.6)
Baseline LED, mg/day	1150.6 (461.6)	1328.1 (498.9)	1411.2 (736.9)	552.0 (188.7)	1016.7 (114.1)	1726.7 (527.7)
UPDRS part II: Activities of daily living during 'on'	17.5 (11.0)	15.5 (10.2)	16.4 (9.9)	17.7 (10.3)	15.5 (10.6)	16.3 (9.3)
UPDRS part III: motor examination during 'on'	23.7 (12.9)	23.9 (11.6)	23.5 (11.6)	25.0 (11.3)	24.7 (12.1)	24.2 (11.9)
UPDRS part IV						
– Modified item 39: 'off' time, h/day	1.3 (0.8)	4.7 (1.1)	9.0 (2.2)	5.5 (3.0)	5.9 (2.8)	6.3 (3.4)
– Modified item 32: time with dyskinesia, h/day	5.6 (4.7)	4.9 (3.7)	3.7 (3.3)	4.3 (3.7)	4.6 (3.4)	4.1 (4.0)
PDQ-8 score	38.9 (18.1)	49.4 (18.0)	46.5 (20.6)	46.8 (19.5)	46.8 (18.3)	46.7 (18.8)

†n = 53.
‡n = 169.
LED: Levodopa equivalent dose; PD: Parkinson's disease; PDQ-8: Parkinson's Disease Questionnaire eight-item; SD: Standard deviation; UPDRS: Unified Parkinson's Disease Rating Scale.

Disease duration subgroups

In both disease duration subgroups, LCIG treatment led to significant ($p < 0.05$ for all visits) improvements in QoL through 24 months of treatment (Figure 2A). Patients with disease duration <10 years at baseline had significant improvements from baseline in ADL at all time points ($p < 0.05$; Figure 2B). Patients with longer disease duration at baseline (≥10 years) experienced significant improvements in ADL from baseline through month 6, but only a trend between months 6 and 18.

'Off' time subgroups

Patients with 3–6 h of 'off' time at baseline and patients with >6 h per day of 'off' time at baseline experienced significant improvements in QoL through month 24 and month 12, respectively ($p < 0.001$ for all; Figure 3A). Patients with <3 h per day of 'off' time at baseline experienced significant improvements in QoL after 6 months of treatment ($p < 0.05$), although changes from baseline were minimal at all other time points. Patients with >6 h per day of 'off' time at baseline experienced significant improvements in ADL through month 12 ($p < 0.01$; Figure 3B). Patients with <3 h per day and patients with 3–6 h of 'off' time at baseline experienced significant improvements ($p < 0.01$) in UPDRS II total scores on the day of discharge, with no statistically significant improvements thereafter. The subgroup of patients with <3 h per day of 'off' time at baseline was small, with 27 or fewer patients at any time point.

LED subgroups

QoL improved significantly at all time points in higher LED subgroups of 800–1200 mg/day and >1200 mg/day ($p < 0.05$ for all; Figure 4A). Patients with an LED below 800 mg/day at baseline experienced significant QoL improvements up to month 6 ($p < 0.05$). Patients with the highest baseline LED (>1200 mg/day) experienced significant improvements in ADL at all time points ($p < 0.01$; Figure 4B).

Safety

Although safety was not assessed in patient subgroups, results from the registry confirmed the established safety profile of LCIG. The safety of LCIG in the full analysis set in the GLORIA registry has been described in detail by Antonini *et al.* [15].

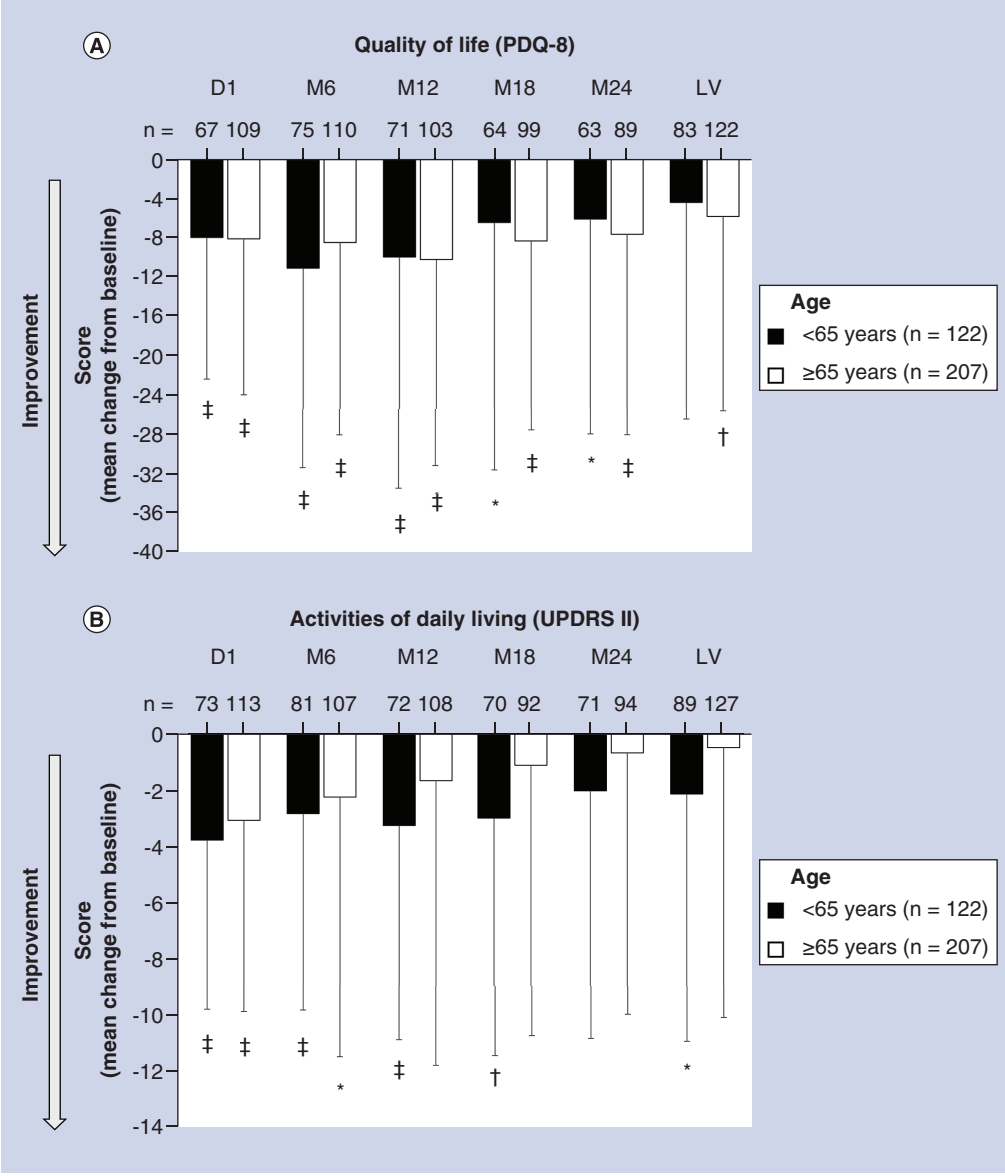

Figure 1. Age subgroup: mean change from baseline in (A) quality of life (PDQ-8 scores) and (B) activities of daily living (UPDRS II scores). Error bars indicate standard deviation. The p-values from a paired *t*-test indicate statistical significance compared with baseline at:
*$p < 0.05$;
†$p < 0.01$;
‡$p < 0.001$.
D1: Discharge from hospital post-percutaneous endoscopic gastrojejunostomy with jejunal extension tube placement; LV: Last visit; M: Month; PDQ-8: Parkinson's Disease Questionnaire eight-item; UPDRS: Unified Parkinson's Disease Rating Scale.

Discussion

Results from this *post hoc* analysis demonstrated that LCIG-related improvements in QoL (>6 point reduction in PDQ-8 total score), are not influenced by patient age and disease duration. Improvements in patients' abilities to perform ADL suggest a greater treatment effect in younger patients (aged <65 years) and patients with a shorter disease duration (<10 years). Age, in general, is negatively correlated with levodopa response [16,17], but this is possibly related to the development of symptoms such as gait and postural instability and cognitive dysfunction, which are poorly responsive to dopamine-replacement therapy [19,20]. The efficacy of LCIG with respect to age has

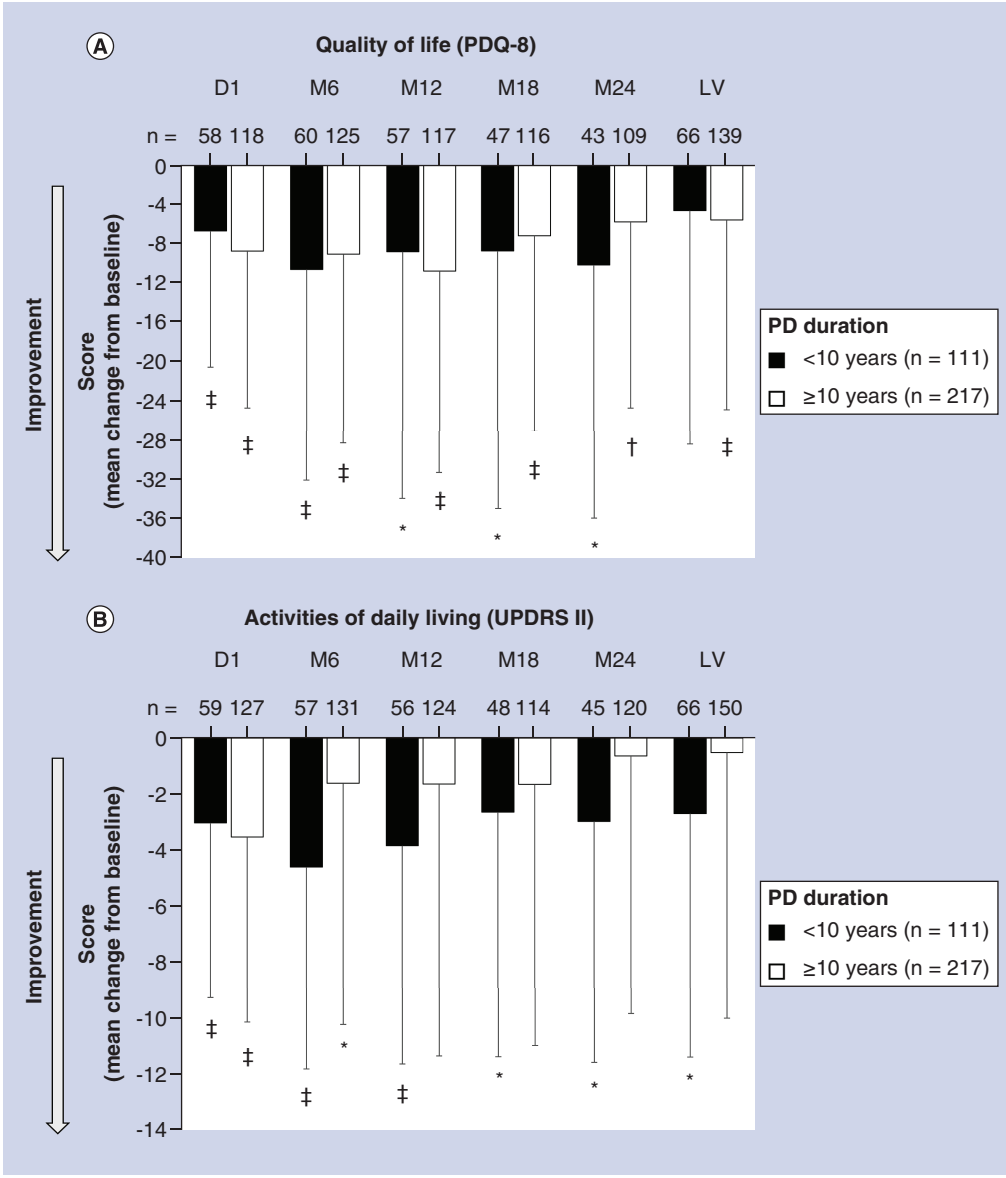

Figure 2. Parkinson's disease duration subgroup: mean change from baseline in (A) quality of life (PDQ-8 scores) and (B) activities of daily living (UPDRS II scores). Error bars indicate standard deviation. The p-values from a paired *t*-test indicate statistical significance compared with baseline at:
*$p < 0.05$;
†$p < 0.01$;
‡$p < 0.001$.
D1: Discharge from hospital post-percutaneous endoscopic gastrojejunostomy with jejunal extension tube placement; LV: Last visit; M: Month; PD: Parkinson's disease; PDQ-8: Parkinson's Disease Questionnaire eight-item; UPDRS: Unified Parkinson's Disease Rating Scale.

been poorly explored and some preliminary reports either indicate reduced benefit in elderly patients [16,17] or no age-related treatment difference [21].

The ability of LCIG to provide similar treatment effects on QoL regardless of a patient's age is important. The efficacy of oral medications in older patients can be compromised by factors such as dysphagia or gastrointestinal dysfunction [22]. Studies of deep brain stimulation have shown age-dependent differences in QoL and risk of adverse events limits its implementation in patients older than 65 years [23–26].

In the GLORIA cohort, improvements in QoL were greater in patients with more 'off' time and higher LED at baseline, suggesting that the magnitude of baseline disability is a predictor of clinical outcome. Improvements in

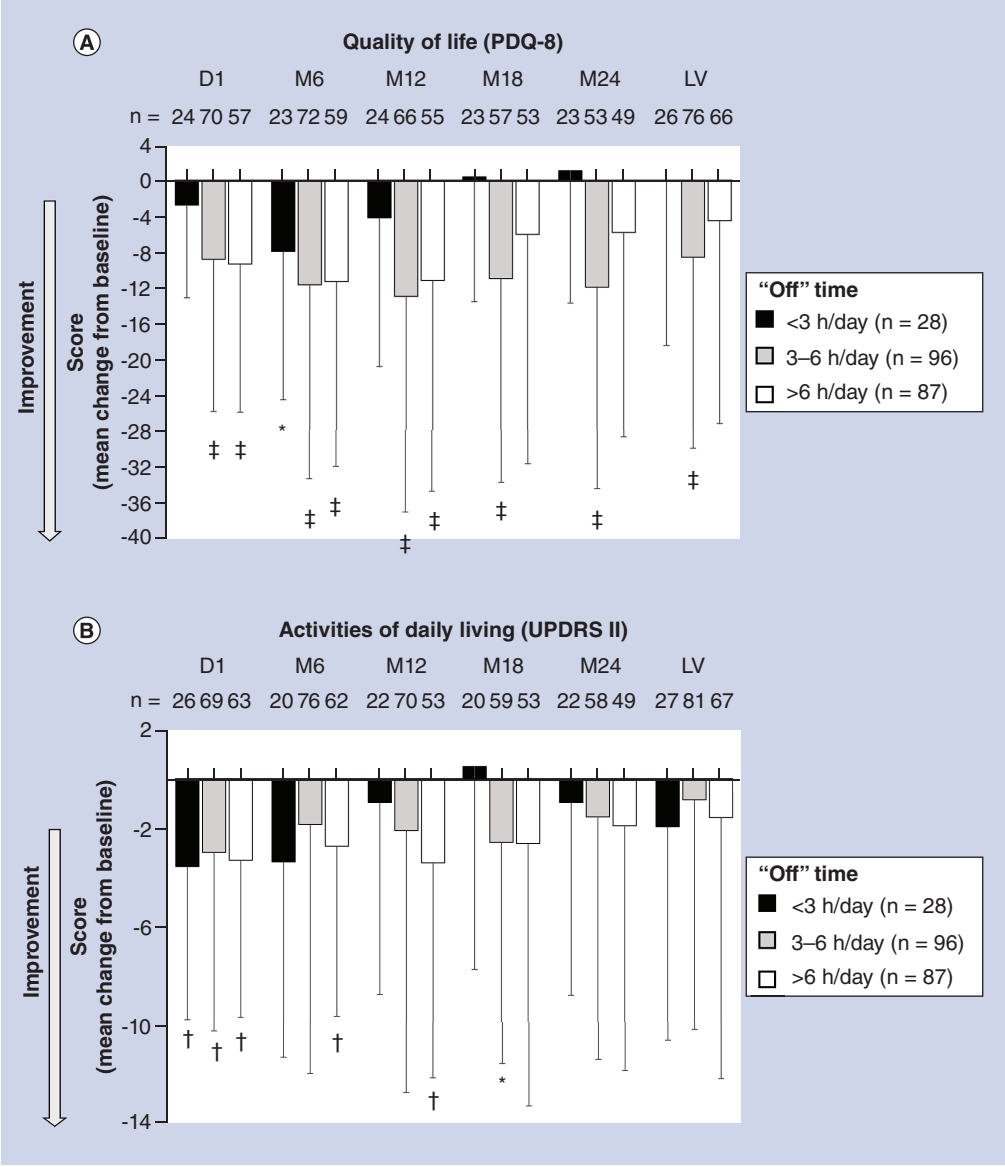

Figure 3. 'Off' time subgroup: mean change from baseline in (A) quality of life (PDQ-8 scores) and (B) activities of daily living (UPDRS II scores). Error bars indicate standard deviation. The p-values from a paired *t*-test indicate statistical significance compared with baseline at:
*$p < 0.05$;
†$p < 0.01$;
‡$p < 0.001$.
D1: Discharge from hospital post-percutaneous endoscopic gastrojejunostomy with jejunal extension tube placement; LV: Last visit; M: Month; PDQ-8: Parkinson's Disease Questionnaire eight-item; UPDRS: Unified Parkinson's Disease Rating Scale.

UPDRS II total scores were of similar magnitude to other open-label routine-care studies where patients experienced 2.6-point reductions in UPDRS II total score after 24 months of LCIG treatment [12], although a prospective trial demonstrated 4.4-point reductions in UPDRS II total scores after 54 weeks of LCIG treatment [7]. We have extended these findings by demonstrating that younger patients and those with shorter disease duration may show similar QoL benefits and potentially greater ADL improvements when compared with older patients and those with longer disease duration, which may provide a justification to consider LCIG early in the advanced PD stage.

These considerations are limited by the *post hoc* nature of the analysis. Although the sizes of some patient subgroups were small (particularly the subgroup of patients with fewer than 3 h of baseline 'off' time), in most cases, it was

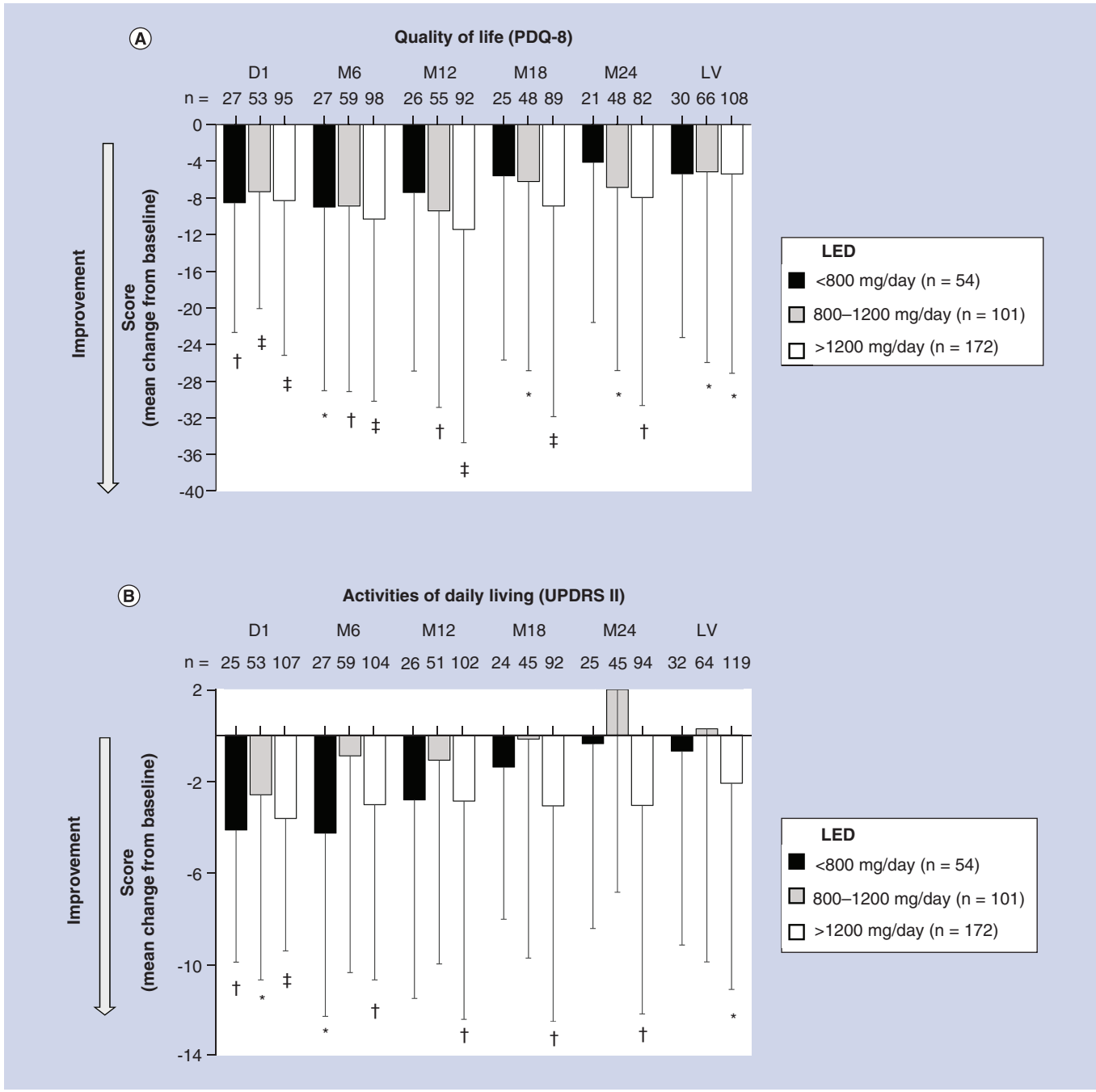

Figure 4. Levodopa equivalent dose subgroup: mean change from baseline in (A) quality of life (PDQ-8 scores) and (B) activities of daily living (UPDRS II scores). Error bars indicate standard deviation. The p-values from a paired *t*-test indicate statistical significance compared with baseline at:
*$p < 0.05$;
†$p < 0.01$;
‡$p < 0.001$.
D1: Discharge from hospital post-percutaneous endoscopic gastrojejunostomy with jejunal extension tube placement; LED: Levodopa equivalent dose; LV: Last visit; M: Month; PDQ-8: Parkinson's Disease Questionnaire eight-item; UPDRS: Unified Parkinson's Disease Rating Scale.

sufficiently large to perform adequate statistical comparisons of the QoL and ADL data. Another limitation is the lack of using a multivariate regression model to assess the potential interactions of the demographics and disease characteristics on QoL and ADL. Motor score changes from baseline (UPDRS part III) were not assessed by subgroup, so it is unknown if improvements in QoL and ADL are related to changes in motor scores. However, UPDRS part III scores demonstrated consistent improvements in motor symptoms over 24 months of treatment in the overall patient population [15]. In addition, patient safety was not assessed by patient subgroups but this has been addressed in detail in the other reports that discuss GLORIA registry data [13,15].

In conclusion, LCIG led to sustained improvements in QoL, irrespective of patient age and disease duration. The magnitude of QoL improvement was greater in patients with more 'off' time and larger LED dose at baseline. Improvements in ADL were observed across all subgroups, but appeared to be greater in patients treated with LCIG earlier in life, after shorter disease duration, and in those with the highest baseline LED. These data may support an early introduction of LCIG in advanced PD.

Author contributions

All authors critically reviewed the manuscript and approved the final version for submission. Concept/design of original research project and data interpretation was done by A Antonini. Concept/design of original research project, statistical analysis and data interpretation was done by WZ Robieson. Concept/design of original research project, data acquisition, statistical analysis and data interpretation was done by L Bergmann. Concept/design of original research project and data interpretation was done by A Yegin. Concept/design of original research project and data interpretation was done by W Poewe.

Financial & competing interests disclosure

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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