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Effects of *GBA1* Variants in Patients With Parkinson's Disease and Levodopa–Carbidopa Intestinal Gel: A Nation-Wide, Multicenter, Longitudinal, "Real-World" Study. The EPIC Study

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ABSTRACT

Background: The outcome of levodopa/carbidopa intestinal gel (LCIG) in Parkinson's disease carriers of *GBA1* mutations (GBA-PD) remains uncertain.

Objective: To evaluate the safety and efficacy of LCIG in a large PD cohort, focusing on *GBA1* variants.

Methods: This multicenter, retrospective, longitudinal "real-world" study included consecutive patients with advanced PD treated with LCIG at 31 Italian centers; data were collected at baseline, 1-, 5-year, and last-available follow-up.

Results: Data from 512 PD patients (59% male, mean age and disease duration at LCIG initiation 67.0 ± 8.0 and 12.9 ± 5.0 years, respectively) were analyzed. *GBA1* genotyping was available for 306 patients (60%), of whom 40 (13%) had *GBA1* mutations or risk variants. Mean follow-up on LCIG was 3.9 ± 2.9 years; 5-year follow-up data were available for 159 subjects. At baseline, GBA-PD had a younger age, shorter PD duration, worse cognition, and more hallucinations than noncarriers. At 1- and 5-year follow-up, LCIG improved motor and non-motor symptoms, OFF-time, and dyskinesias in the entire population. In GBA-PD, MDS-UPDRS parts I, II, and III scores did not change, while part IV score improved significantly less than in noncarriers; cognition

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and orthostatic hypotension symptoms worsened more rapidly. Multivariate analysis of predictors for adverse events and LCIG discontinuation found no significant contribution from *GBA1* mutation status.

Conclusions: *GBA1* status does not increase the risk of adverse events or LCIG discontinuation. LCIG is a safe option for advanced GBA-PD, even in patients with cognitive impairment at baseline. However, GBA-PD experiences lower efficacy on motor disability and complications and faster cognitive decline than noncarriers.

1 | Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by disabling motor and non-motor symptoms (NMS) [1]. Heterozygous mutations in the *GBA1* gene represent the most frequent genetic risk factor for PD [2–4]. PD carriers of *GBA1* mutations (GBA-PD) progress more rapidly, with earlier cognitive dysfunction and psychosis, greater substantia nigra terminal loss, and reduced survival [5]. Given the more rapid progression of both motor and non-motor disability in GBA-PD [4–6], it remains debated whether *GBA1* mutation carriers respond differently in terms of efficacy and safety to device-aided therapies, such as deep brain stimulation of the subthalamic nucleus (STN-DBS) and continuous levodopa infusion strategies [7–10]. Levodopa/carbidopa intestinal gel (LCIG) is a commonly chosen procedure in patients with advanced PD not adequately compensated by medical therapy, as it allows continuous levodopa delivery into the small intestine via percutaneous endoscopic gastrojejunostomy (PEG-J) to maintain more stable plasma levodopa concentration and therefore improve motor and non-motor fluctuations [11–13]. GBA-PD patients may particularly benefit from LCIG due to its favorable cognitive and psychiatric outcomes, especially for those with cognitive impairment at baseline. To date, no studies have evaluated the safety and efficacy of LCIG in large GBA-PD cohorts compared to noncarriers.

In this scenario, the EPIC (Effects of *GBA1* variants in patients with Parkinson's dIsease and LCIG) study aims to evaluate the safety and efficacy of LCIG in a large cohort of advanced PD patients, focusing on the comparison between GBA-PD versus noncarriers. These results may assist neurologists in the decision-making process determining the eligibility of GBA-PD for subcutaneous levodopa infusion therapy, which promises broader applicability than DBS or LCIG due to its simpler management in secondary and tertiary care settings.

2 | Methods

2.1 | Participants

This is a multicenter, retrospective, longitudinal "real-world" study involving 31 secondary and tertiary movement disorders referral centers throughout Italy, including and expanding the PARKNET cohort (Figure S1) [10, 14]. We included patients with clinically established PD [15], who consecutively initiated treatment with LCIG for disabling motor fluctuations and/or dyskinesias, irrespective of genetic testing. We excluded patients with (i) other device-aided therapies (DBS or continuous subcutaneous apomorphine infusion), (ii) atypical or secondary parkinsonism, and (iii) incomplete clinical data.

2.2 | Data Collected

Movement disorders specialists at each participating center reviewed demographic and clinical data from medical records of all consecutive PD patients who initiated LCIG treatment between 2005 and 2023 and whose detailed clinical data were available at baseline (from day −1 to day −90 prior to LCIG initiation) and at least one follow-up visit (see Appendix S1). When available, efficacy and safety data were additionally collected at 60 ± 12 months after LCIG initiation and at the last available assessment (limited to safety, last visit censored up to 10 years; defined as "long term"). In cases of early dropouts (< 9 months after LCIG initiation), only safety data were included in the analysis.

Safety data during LCIG were previously collected by neurologists with expertise in device-aided therapies and documented in the medical record. We documented all adverse events (AEs), which were defined as all events with a reasonable possibility of being caused by the device (related to tube or PEG-J, including any perioperative complication) or treatment (subdivided into motor- and non-motor-related) or other types, as recorded by the clinician.

2.3 | Objectives and Study Outcomes

We used a two-step approach: first, we investigated long-term safety and efficacy in a large cohort of consecutive PD treated with LCIG; then, we focused on the effects of *GBA1* mutation status in an unbiased subpopulation of PD patients who underwent genetic testing. The primary objective was to investigate the safety of LCIG treatment over 12 months, focusing on the rate and causes of discontinuation based on *GBA1* mutation status. Secondary objectives were to: (i) assess the effectiveness at 1- and 5-year follow-up in controlling motor complications in GBA-PD versus noncarriers; (ii) examine differences in clinical history (age and disease duration at LCIG initiation) according to *GBA1* status; (iii) determine the role of *GBA1* status in predicting AEs at long-term follow-up; and (iv) evaluate the overall safety and efficacy of LCIG in the entire PD cohort, irrespective of genetic status.

2.4 | Ethics

The study was approved by the ethics committee of each participating center (coordinating center Ethics Committee: Neurological Institute Carlo Besta, Milan; CE n°32/2023). Concerning the PARKNET consortium: Project code: PARK-Net 3-22033-ID 3951. This study was conducted in accordance with the declaration of Helsinki, including written informed consent to the use of patient anonymized clinical data for research purposes according to local regulatory requirements.

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2.5 | Statistical Analysis

Given the nature of the study, no specific sample size calculation was conducted. However, given the prevalence of *GBA1* variants in the overall PD population (approximately 10%–15%) [16–18], we estimated that the inclusion of about 300 patients would have enabled a reasonable comparison of safety data between GBA-PD and noncarriers. Specifically, choosing a non-inferiority margin of 10% and supposing a LCIG discontinuation rate for GBA-PD and PD noncarriers of 35% and 25% [19, 20], respectively, for achieving an 80% power at the 5% level of significance, the sample size for GBA-PD and noncarriers are 40 and 264, respectively. Patients who completed at least 24 h on LCIG infusion were included in the safety population. The occurrence of AEs was investigated by multivariable logistic regression. Cox's multivariable regression models were used to address treatment discontinuation. At the group level, a comparison of continuous and categorical data between time points was conducted with the paired *t* test or McNemar's test, respectively. Changes in variables at 1 year and over multiple time points were also analyzed using an adjusted mixed model for repeated measures. Analyses were performed with the software STATA 17 (StataCorp, College Station, TX, USA). Two-tailed *p* values <0.05 indicated statistical significance. Further details are available in Appendix S1.

3 | Results

We collected data on 634 PD patients, of whom 119 were excluded due to incomplete clinical data and 3 due to exclusion criteria (see flowchart in Figure 1). A total of 512 PD subjects were suitable for statistical analysis, distributed as follows: noncarriers ($N=306$), GBA-PD ($N=40$), and *GBA1* mutation status not available (genetic test not performed, $N=206$). Distribution of GBA1 mutations and risk variants is reported in Table S1. Demographic and clinical features of patients with undetermined *GBA1* status were comparable to those of PD noncarriers (data not shown), as expected by the predicted 85%–90% noncarrier prevalence. This group was included in the analyses of the entire population but excluded from those focusing on *GBA1* mutation status.

Of the 512 individuals who initiated LCIG, 31 (6.1%) discontinued LCIG before 9 months and were included in the safety analysis, but not in the efficacy analysis. Data at the 1- and 5-year follow-up assessments were available for 481 and 159 patients, respectively. The median daily duration of LCIG infusion was 16 h; only six patients were receiving 24-h therapy at their last visit (1.2%, one GBA-PD and five noncarriers).

Baseline data are shown in Table 1 and are detailed in the Supporting Information.

3.1 | Safety of LCIG

Frequencies and causes of discontinuation and AEs in the entire PD population as well as in GBA-PD versus noncarriers are provided in Table 2, while predictors of AEs are reported in Table 3.

3.1.1 | Discontinuation Rate

A total of 191 out of 512 patients (37.3%) discontinued LCIG after a median of 86 months (corresponding to 7.2 years), of whom 31 (6%) after ≤ 9 months. LCIG was discontinued due to device-related (5.7%), treatment-related (7.0%), and other (8.6%) causes, including limited efficacy in 2.9% of patients or death (Table 2). Eighty-two deaths (16%) were registered during LCIG infusion, one of which was deemed probably related to the device. Concerning the primary endpoint, we found no difference in frequency or causes of discontinuation between GBA-PD and noncarriers. Multivariate analysis of predictors of LCIG discontinuation during the follow-up (adjusted Cox regression model) excluded an effect of *GBA1* status in the long-term (HR = 1.30 [95% CI, 0.76–2.24], $p=0.34$; Figure 2A), including the effects of severe versus mild/risk *GBA1* variants (HR = 1.33 [95% CI, 0.63–2.81], $p=0.45$; HR = 1.27 [95% CI, 0.63–2.58], $p=0.49$, respectively; Figure 2B).

3.1.2 | Adverse Events

During the follow-up period, 259 (50.6%) patients experienced at least one AE, of whom 17 had a serious AE (17/512, 3.3%) requiring admission to hospital or leading to death. Overall, a total of 316 AEs were reported, of which 216 were device-related, 52 were treatment-related, and 47 had other causes. Among device-related AEs, 23.2% of patients reported PEG-J-related AEs and 18.9% reported tube complications. Concerning treatment-related AEs, the rate of non-motor complications (agitation, confusional states, hallucinations, OH symptoms) was similar between GBA-PD and noncarriers. Logistic regression analysis of predictors showed that any-type AEs were associated with older age and greater motor disability (according to HY stage) at LCIG initiation and comorbidities; device-related AEs were associated with age at LCIG initiation and comorbidities; treatment-related AEs were associated with PD duration at LCIG initiation. *GBA1* status was not correlated to any AEs (Table 3).

3.2 | Efficacy of LCIG

At 1-year follow-up, data were available for 481 patients, of whom 252 were noncarriers and 38 were GBA-PD subjects, and 191 had undetermined *GBA1* mutation status (Table 4). Efficacy data on the entire PD population are reported in the Supporting Information.

3.2.1 | GBA-PD Versus Noncarriers

At 1-year follow-up, LCIG improved all MDS-UPDRS scores from part I to part IV in noncarriers, where GBA-PD significantly improved only on part IV score (including subscores on dyskinesias and motor fluctuations; Table 4). Time–group interaction showed that the difference in MDS-UPDRS parts II and IV scores (including dyskinesias and motor fluctuations subscores) was significantly different between GBA-PD and noncarriers. Concerning NMS, cognitive functions and OH symptoms worsened faster in GBA-PD than noncarriers (Table 4).

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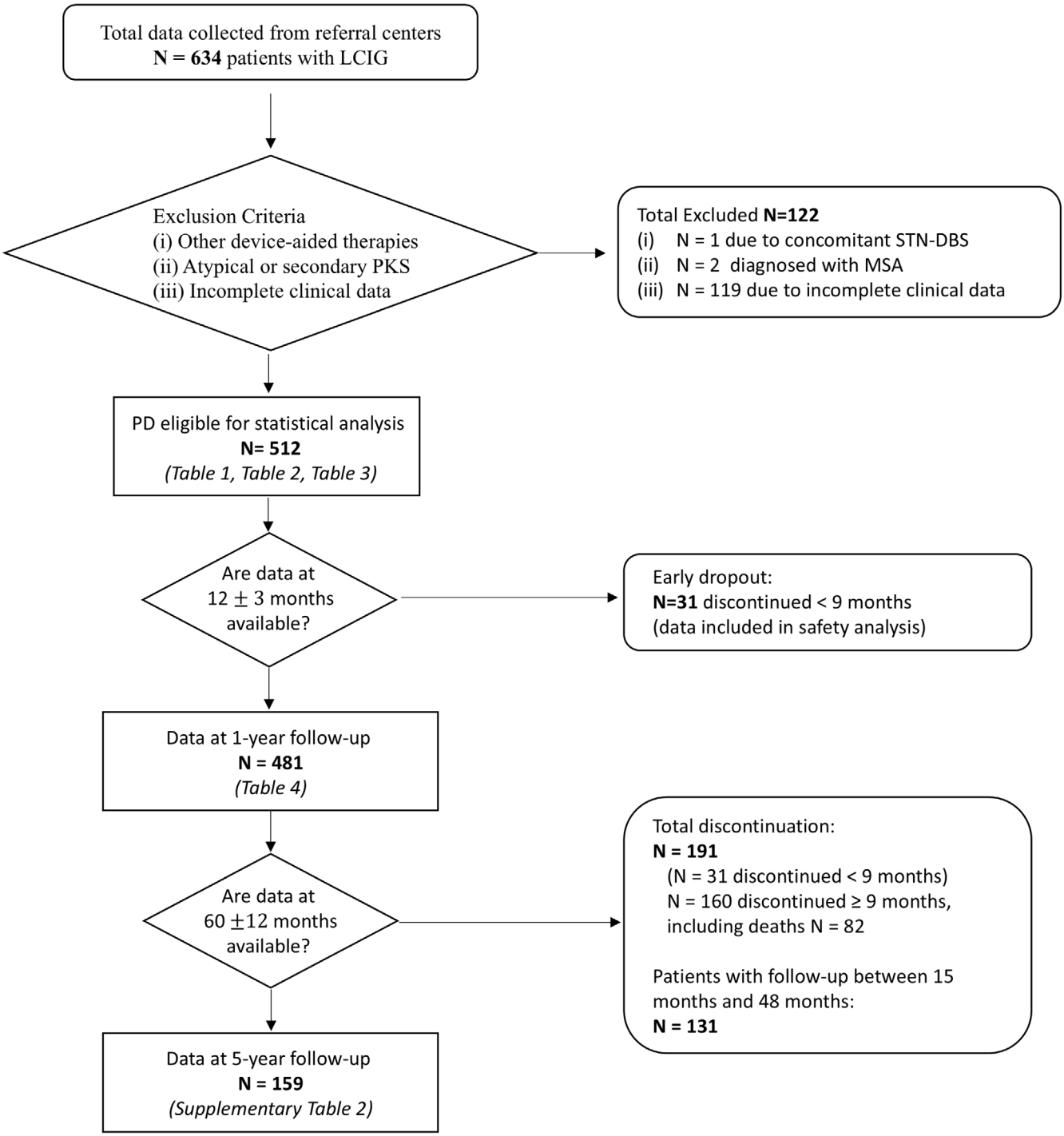

FIGURE 1 | Study flowchart.

Data at 5-year follow-up are reported on Table S2. Group–time interaction was significant for MDS-UPDRS part I ($p = 0.012$), part II ($p = 0.020$), and part IV ($p < 0.001$) scores, consistent with a faster decline in GBA-PD than noncarriers. Compared to baseline, MDS-UPDRS part IV subscores for dyskinesias worsened in GBA-PD after 1 year, whereas it remained stable in noncarriers. In GBA-PD, MDS-UPDRS part IV subscores for motor fluctuations increased at the 5-year compared to the 1-year follow-up, returning to baseline levels. In contrast, noncarriers maintained significantly improved motor fluctuations scores compared to baseline even after 5 years from LCIG initiation (group–time interaction $p < 0.001$ and $p = 0.003$, respectively). Although cognitive functions, hallucinations/psychosis, depression/anxiety, RBD, and OH symptoms worsened over time in both groups, RBD and OH progressed more in GBA-PD than in noncarriers (group–time interaction $p = 0.042$ and $p = 0.048$, respectively). Interestingly, prevalence of PNP increased more in noncarriers than GBA-PD (group–time interaction $p = 0.020$). Unadjusted prevalence of cognitive impairment and selected motor outcome measures at baseline, 1- and 5-year follow-up visits in GBA-PD versus PD noncarriers are shown in Figure 3.

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TABLE 1 | Clinical and treatment characteristics of the study population.

Variable	Total population (*N* = 512)	GBA-PD (*N* = 40)	Noncarriers (*N* = 266)	*p*[g]	Not available (*N* = 206)
Sex (male), *N* (%)	302 (59.0)	21 (52.5)	157 (59.0)	0.49	124 (60.2)
Positive family history (first-degree), *N* (%)	120 (23.4)	10 (25.0)	57 (27.6)	0.68	53 (25.7)
Body weight (kg), mean [SD]	69.1 [13.6]	66.9 [10.6]	69.2 [14.1]	0.32	69.4 [13.4]
Tremor-dominant motor phenotype, *N* (%)	225 (43.9)	12 (30.0)	108 (40.6)	0.23	105 (51.0)
Non-motor symptoms at onset, *N* (%)	280 (55.1)	28 (70.0)	138 (51.9)	**0.040**	114 (55.3)
Depression and/or anxiety, *N* (%)	118 (23.0)	11 (27.5)	68 (25.5)	0.85	39 (18.9)
RBD, *N* (%)	79 (15.4)	9 (22.5)	38 (14.3)	0.24	32 (15.5)
Constipation, *N* (%)	86 (16.8)	10 (25.0)	39 (14.7)	0.11	37 (17.9)
Hyposmia, *N* (%)	95 (18.6)	8 (20.0)	44 (16.5)	0.65	43 (20.8)
Age at onset (years), mean [SD]	54.1 [8.7]	50.1 [10.0]	54.1 [9.0]	**0.011**	54.9 [7.8]
Age at LCIG initiation (years), mean [SD]	67.0 [8.0]	61.1 [9.3]	67.1 [8.2]	**< 0.001**	68.1 [7.0]
Age at last visit (years), mean [SD]	70.3 [11.2]	65.3 [11.2]	70.0 [12.1]	**0.022**	71.8 [9.4]
Disease duration at LCIG initiation (years), mean [SD]	12.9 [5.0]	11.0 [4.3]	13.0 [5.2]	**0.021**	13.2 [4.6]
Disease duration at last visit (years), mean [SD]	16.9 [6.2]	15.2 [6.8]	16.8 [6.3]	0.13	17.3 [5.7]
Duration of LCIG treatment (years), mean [SD]	3.9 [2.9]	4.0 [3.1]	3.8 [2.6]	0.79	4.0 [2.6]
MDS-UPDRS score at LCIG initiation[a]					
Part I, mean [SD]	12.7 [6.1]	15.1[7.9]	13.5 [6.5]	0.25	11.5 [5.0]
Part II, mean [SD]	16.9 [7.6]	16.3 [9.2]	17.5 [7.8]	0.40	16.3 [7.1]
Part III, mean [SD]	32.9 [14.7]	29.7 [16.5]	32.8 [15.4]	0.25	33.6 [13.3]
Part IV (motor complications), mean [SD]	9.8 [3.4]	10.5 [3.6]	10.4 [3.6]	0.92	9.0 [2.9]
Motor complications at LCIG initiation					
Dyskinesias score[b], mean [SD]	3.1 [1.9]	3.4 [1.6]	3.3 [1.9]	0.66	2.9 [1.8]
Dyskinesias, *N* (%)	416 (81.3)	32 (80.0)	215 (80.8)	0.83	169 (82.0)
Complex/atypical dyskinesias, *N* (%)	126 (24.6)	9 (22.5)	57 (21.4)	0.84	60 (29.1)
OFF state[b], mean [SD]	6.7 [2.4]	7.0 [2.6]	7.2 [2.5]	0.72	6.2 [2.2]
Fluctuations, *N* (%)	488 (95.3)	39 (97.5)	249 (93.6)	0.49	200 (97.1)

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TABLE 1 | (Continued)

Variable	Total population (*N* = 512)	GBA-PD (*N* = 40)	Noncarriers (*N* = 266)	*p*[g]	Not available (*N* = 206)
Dopaminergic deficiency score[c], mean [SD]	18.4 [7.8]	16.3 [7.7]	18.8 [8.4]	0.13	18.3 [7.0]
Nondopaminergic deficiency score[c], mean [SD]	4.6 [2.9]	5.1 [3.4]	5.1 [2.8]	0.90	4.0 [2.6]
Hoehn–Yahr stage, mean [SD]	2.8 [0.8]	2.9 [1.0]	2.8 [0.8]	0.39	2.8 [0.7]
≥ 3, *N* (%)	306 (59.8)	25 (62.5)	153 (57.5)	0.61	128 (62.1)
Non-motor symptoms					
Cognitive impairment[d], *N* (%)	213 (41.6)	22 (55.0)	102 (38.3)	0.057	89 (43.2)
MDS-UPDRS—item 1.1, mean [SD]	0.7 [0.8]	1.2 [0.9]	0.7 [0.8]	**0.013**	0.6 [0.8]
MoCA score, mean [SD]	23.0 [5.1]	20.4 [5.3]	23.4 [5.0]	**0.002**	23.1 [5.1]
FAB score, mean [SD]	14.3 [3.3]	12.1 [3.8]	14.6 [3.1]	**0.004**	14.3 [3.2]
Hallucinations and psychosis, *N* (%)	123 (24.0)	18 (45.0)	63 (23.7)	**0.007**	42 (20.4)
MDS-UPDRS—item 1.2, mean [SD]	0.4 [0.7]	0.9 [1.0]	0.4 [0.6]	**0.006**	0.4 [0.7]
Depression and/or anxiety, *N* (%)	317 (61.9)	29 (72.5)	152 (57.1)	0.084	136 (66.0)
MDS-UPDRS—item 1.3 + item 1.4, mean [SD]	2.6 [1.6]	3.2 [1.3]	2.8 [1.9]	0.17	2.4 [1.3]
Impulse control disorders, *N* (%)	111 (21.7)	14 (35.0)	55 (20.7)	0.065	42 (20.4)
REM sleep behavior disorder, *N* (%)[e]	207 (40.4)	19 (47.5)	101 (38.0)	0.30	87 (42.2)
Sleep problems MDS-UPDRS—item 1.7, mean [SD]	1.5 [1.0]	1.7 [1.3]	1.6 [0.9]	0.84	1.4 [0.9]
Pain MDS-UPDRS—item 1.9 + 4.6, mean [SD]	1.5 [1.8]	1.8 [1.7]	1.9 [1.8]	0.65	1.1 [1.8]
Urinary problems MDS-UPDRS—item 1.10, mean [SD][f]	1.2 [1.0]	1.3 [0.9]	1.2 [1.0]	0.62	1.3 [0.9]
Orthostatic hypotension, *N* (%)	86 (16.8)	7 (17.5)	40 (15.0)	0.64	39 (18.9)
MDS-UPDRS—item 1.12, mean [SD]	0.7 [0.9]	0.9 [1.0]	0.7 [0.9]	0.53	0.7 [0.8]
Non-levodopa-responsive symptoms					
Dysphagia, *N* (%)	70 (13.7)	3 (7.5)	38 (7.4)	0.32	29 (14.1)
MDS-UPDRS—item 2.2 + 2.3, mean [SD]	1.5 [1.4]	1.4 [1.4]	1.6 [1.4]	0.48	1.4 [1.4]
Frequent falls, *N* (%)	177 (34.6)	9 (22.5)	97 (36.4)	0.11	71 (34.5)
MDS-UPDRS—item 2.12, mean [SD]	1.8 [0.9]	1.7 [1.1]	1.8 [0.9]	0.59	1.8 [0.8]
Freezing of gait, *N* (%)	334 (65.2)	21 (52.5)	151 (56.8)	0.61	158 (76.7)

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TABLE 1 | (Continued)

Variable	Total population ($N=512$)	GBA-PD ($N=40$)	Noncarriers ($N=266$)	p^g	Not available ($N=206$)
MDS-UPDRS—item 2.13, mean [SD]	1.5 [1.0]	1.2 [1.1]	1.6 [1.1]	0.10	1.6 [1.0]
Postural instability, *N* (%)	231 (45.1)	19 (47.5)	130 (48.9)	0.99	82 (39.8)
MDS-UPDRS—item 3.12, mean [SD]	1.5 [1.0]	1.5 [1.0]	1.5 [1.1]	0.66	1.4 [0.9]
Posture abnormalities, *N* (%)	168 (32.8)	14 (35.0)	70 (26.3)	0.26	84 (40.8)
MDS-UPDRS—item 3.13, mean [SD]	1.7 [0.9]	1.4 [0.9]	1.7 [0.9]	0.16	1.8 [0.9]
Peripheral neuropathy, *N* (%)	69 (13.5)	5 (12.5)	29 (10.9)	0.79	35 (17.0)
Therapy at baseline					
Dopaminergic medications					
Total daily oral Levodopa dose (mg/day), mean [SD]	809 [381]	763 [351]	779 [404]	0.81	857 [347]
Concomitant MAO-B inhibitors, *N* (%)	173 (33.8)	13 (32.5)	100 (37.6)	0.60	60 (29.1)
Concomitant COMT inhibitors, *N* (%)	192 (37.5)	15 (37.5)	107 (40.2)	0.86	70 (34.0)
Concomitant DA, *N* (%)	343 (67.0)	25 (62.5)	178 (66.9)	0.59	140 (68.0)
LED from DA (mg/day), mean [SD]	156 [188]	136 [145]	152 [195]	0.62	166 [185]
Total-LED (mg/day), mean [SD]	1174 [528]	1140 [521]	1141 [551]	0.98	1224 [493]
Nondopaminergic medications					
Amantadine, *N* (%)	88 (17.2)	11 (27.5)	47 (17.7)	0.19	30 (14.6)
Anticholinergics, *N* (%)	16 (3.1)	0 (0.0)	8 (3.0)	0.99	8 (3.9)
Antidepressants, *N* (%)	173 (33.8)	17 (42.5)	92 (34.6)	0.38	64 (31.1)
Antipsychotics, *N* (%)	97 (18.9)	16 (40.0)	47 (17.7)	**0.003**	34 (16.5)
Antidementia, *N* (%)	16 (3.1)	3 (7.5)	9 (3.4)	0.20	4 (1.9)
Anti-orthostatic hypotension, *N* (%)	18 (3.5)	3 (7.5)	5 (1.9)	0.073	10 (4.8)

Abbreviations: COMT, catechol-O-methyltransferase; DA, dopamine agonists; iMAO-B, MonoAmine Oxidase type B Inhibitors; IR, levodopa immediate release; LED, levodopa equivalent dose; MDS-UPDRS, International Parkinson and Movement Disorders Society Unified Parkinson's Disease Rating Scale; SD, standard deviation. Note: Bold values are statistically significant ($p < 0.05$).

[a]In "ON" condition.

[b]Dyskinesia is defined as the sum of MDS-UPDRS IV items 4.1 + 4.2, whereas OFF is the sum of items 4.3 + 4.4 + 4.5 + 4.6.

[c]Modified version of the motor examination scores proposed by Levy et al. [Supplementary Reference 4 in Appendix S1] adapted to the MDS-UPDRS: Dopaminergic score: sum of items 3.2 + 3.3 + 3.5 + 3.6 + 3.8 + 3.17 + 3.18; non-dopaminergic score: sum of items 3.1 + 3.9 + 3.10 + 3.12 + 3.13.

[d]Diagnosis of mild cognitive impairment or dementia [Supplementary References 2 and 3 in Appendix S1, respectively].

[e]RBD should be considered as "*probable* RBD" as it was diagnosed using videopolysomnography only in a subset of patients.

[f]OH was defined according to consensus criteria [21] because instrumental assessment was not available at the majority of clinical centers.

[g]GBA vs. noncarriers, according to parametric or nonparametric tests (continuous variables) or Fisher's exact test (categorical variables) as appropriate.

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TABLE 2 | Frequency and causes of discontinuation of LCIG infusion and adverse events according to GBA status.

Safety variable	Total population (*N* = 512)	GBA-PD (*N* = 40)	Noncarriers (*N* = 266)	*p*[a,b] (GBA vs. noncarriers)	Genetic status not available (*N* = 206)
Discontinuation of LCIG, *N* (%)	191 (37.3)	18 (45.0)	83 (31.2)	0.08	90 (43.7)
Time to discontinuation (months), median [95% CI][a]	86 [78–95]	70 [40–70]	92 [67–106]	0.12	82 [66–95]
Early (< T1[c]), *N* (%)	31 (6.1)	2 (5.0)	14 (5.3)	0.62	15 (7.3)
At efficacy evaluation (T1[d]), *N* (%)	34 (6.6)	2 (5.0)	14 (5.3)	0.62	18 (8.7)
Causes of discontinuation, *N* (%)					
Device-related	29 (5.7)	0 (0.0)	12 (4.5)	0.83	17 (8.3)
Treatment-related	36 (7.0)	4 (10.0)	13 (4.9)	0.17	19 (9.2)
Other causes	44 (8.6)	5 (12.5)	24 (9.0)	0.34	15 (7.3)
Limited/no efficacy	15 (2.9)	0 (0.0)	7 (2.6)	0.68	8 (3.9)
Deaths[e]	82 (16.0)	9 (22.5)	34 (12.8)	0.08	39 (18.9)
Total adverse event, *N*	316	21	141	—	154
Patients reporting at least one event, *N* (%)	259 (50.6)	19 (47.5)	116 (43.6)	0.38	124 (60.2)
Patients reporting two or more events, *N* (%)	74 (14.5)	4 (10.0)	33 (12.4)	0.57	37 (18.0)
Patients reporting serious adverse events, *N* (%)	17 (3.3)	1 (2.5)	5 (1.9)	0.36	11 (5.3)
Fatal, *N* (%)	1 (0.2)	0 (0.0)	0 (0.0)	0.99	1 (0.5)
Total AEs device-related, *N*	216	7	111	—	92
Patients reporting tube complications, *N* (%)	97 (18.9)	6 (15.0)	47 (17.7)	0.58	44 (21.4)
Patients reporting PEG-J-related, *N* (%)	119 (23.2)	7 (17.5)	64 (24.1)	0.76	48 (23.3)
Peri-operative (any-type device-related), *N* (%)	46 (9.0)	1 (2.5)	25 (9.4)	0.87	20 (9.7)
Total AEs treatment-related, *N*	53	5	18	—	30
Patients reporting motor-related, *N* (%)	23 (4.5)	2 (5.0)	4 (1.5)	0.19	17 (8.3)
Patients reporting non-motor-related, *N* (%)	30 (5.9)	3 (7.5)	14 (5.3)	0.42	13 (6.3)
Total AEs other types, *N*	47	3	12	—	32

[a]For non-inferiority calculated using the Kaplan–Meier method (*p*-value according to Logrank test).
[b]For non-inferiority calculated using the Fisher's exact test unless otherwise indicated.
[c]Early discontinuation defined as LCIG discontinuation < 9 months (before T1).
[d]T1 ranges between 9 and 15 months.
[e]One (1.2%) death was deemed probably related to the device, while the others (98.8%) unrelated to the device or to LCIG treatment and were due to other causes.

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TABLE 3 | Associations (logistic regression analysis) between baseline characteristics and adverse events.

	Any-type ($N=135$)		Device-related ($N=102$)		Treatment-related ($N=22$)	
Independent variables	**OR [95% CI]**	***p***	**OR [95% CI]**	***p***	**OR [95% CI]**	***p***
Male gender	0.61 [0.36–1. 20]	0.061	0.60 [0.35–1.02]	0.059	1.46 [0.54–3.94]	0.46
Age at LCIG initiation (years)	0.96 [0.93–0.99]	**0.012**	0.97 [0.94–0.99]	**0.031**	0.98 [0.94–1.03]	0.50
Disease duration at LCIG initiation (years)	0.99 [0.95–1.04]	0.80	1.03 [0.98–1.08]	0.28	0.87 [0.93–0.98]	**0.019**
Comorbidity (≥1 vs. none)	4.36 [2.56–7.44]	**<0.001**	3.36 [1.92–5.88]	**<0.001**	2.17 [0.79–5.97]	0.13
Hoehn–Yahr stage ≥3	0.59 [0.35–0.98]	**0.043**	0.72 [0.43–1.22]	0.22	0.80 [0.32–2.00]	0.64
Cognitive impairment (yes)[a]	1.40 [0.84–2.32]	0.19	1.45 [0.86–2.44]	0.16	1.00 [0.40–2.51]	0.99
GBA status						
Noncarrier	1.00 (reference)		1.00 (reference)		1.00 (reference)	
Carrier	0.92 [0.44–1.95]	0.84	0.69 [0.32–1.51]	0.36	1.66 [0.54–5.13]	0.38

[a]Mild cognitive impairment (PD-MCI) or dementia (PDD) according to MDS criteria.

4 | Discussion

This multicenter study supports the long-term effectiveness of LCIG in managing motor fluctuations, dyskinesia, and motor and non-motor aspects of experiences of daily living in a large, "real-world" cohort of advanced PD patients. Focusing on the effects of *GBA1* mutation status, there are two main findings to highlight. (1) *Safety*: *GBA1* status did not significantly influence the rate or causes of AEs or the long-term discontinuation rate over a follow-up period up to 10 years. (2) *Efficacy*: although LCIG significantly improved motor fluctuations and dyskinesias in both GBA-PD and noncarriers, the magnitude of such improvement was significantly smaller in GBA-PD.

As *precision medicine* advances, integrating genotype and phenotype into decision-making for device-aided therapies has major implications for managing advanced PD. While continuous levodopa infusion is a safe and feasible option in GBA-PD, neurologists, patients, and caregivers should be aware of the potential suboptimal therapeutic response and faster disease progression, adjusting their expectations accordingly.

The "real-world" design of this study minimizes the risk of significant selection or inclusion bias, supporting the representativeness of the cohort. This is further reflected by the 13% prevalence of pathogenic heterozygous *GBA1* variants, which aligns with the global range of 10%–14% [16–18]. Our data confirm that GBA-PD present with an earlier age at onset, greater burden of NMS, and develop disabling motor fluctuations and dyskinesias earlier than noncarriers [3–5, 10]. Accordingly, they are eligible to device-aided therapies more frequently [5], at younger age and earlier during the course of disease than noncarriers [3, 4, 10, 22]. Ultimately, the decision to triage and refer GBA-PD patients for DBS or infusion therapies should be tailored to individual clinical profiles [6, 7, 23].

4.1 | Safety of LCIG

4.1.1 | Discontinuation Rate

In our cohort, the discontinuation rate was 37.3% over a 10-year observation period. These data overlap with the 34% of a previous study on 86 PD patients followed for 4.1 years [19]. In a study of 103 PD patients treated with LCIG for an average of 5 years, the discontinuation rate exceeded ours: 47.6% discontinued due to death (including two related to LCIG), one-third due to advanced dementia and/or neuropsychiatric issues, and 16% due to device dissatisfaction [24]. In another cohort of 98 PD patients, a lower discontinuation rate of 18.4% (26% including deaths) over a mean observation time of 2.6 years was reported, identifying disease duration at baseline as the only significant predictor of discontinuation [25]. We recorded 82 deaths (16%), only one of which (0.2%) was considered "possibly related" to the LCIG system. This estimate is in line with a previous integrated safety investigation of LCIG prospective clinical trials [26, 27], supporting the overall safety of this device-aided therapy. The median rate of LCIG discontinuation varies considerably in published literature according to whether deaths are included [19, 20, 24, 28] or not [13, 25, 29], ranging from 7% [13] to 54.4% [20]. The EPIC study had an average duration of observation during LCIG infusion of nearly 4 years and a follow-up ranging up to 10 years. We overcame this issue by using a robust safety primary endpoint whose collection was reliable, such as the discontinuation rate. Considering that death, neuropsychiatric problems, and dementia are natural causes for discontinuation when PD progresses, and the higher risk for all these features in GBA-PD is largely established [3–5], it is of utmost importance to establish that *GBA1* mutation status is not an independent factor of discontinuation and AEs per se. Therefore, the take-home message of this study is that *GBA1* mutation status did neither predict treatment discontinuation nor AEs, and this applied also after stratifying the GBA-PD population according to the severity of *GBA1* mutation.

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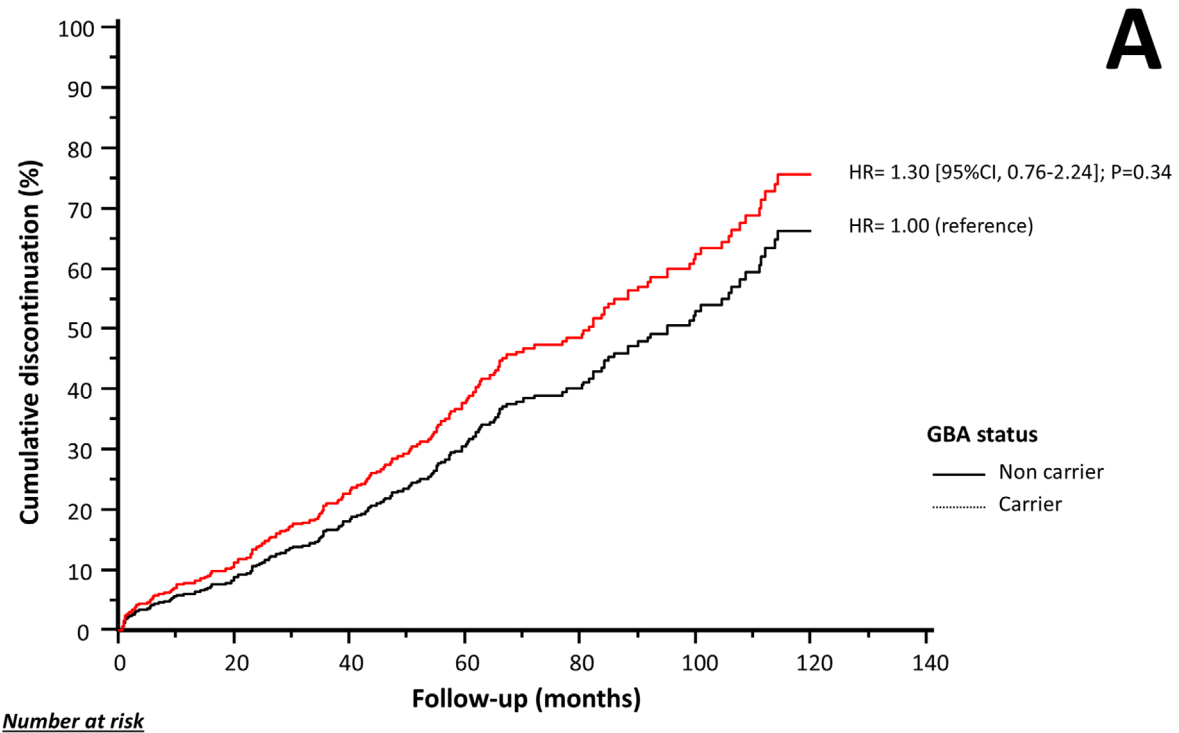
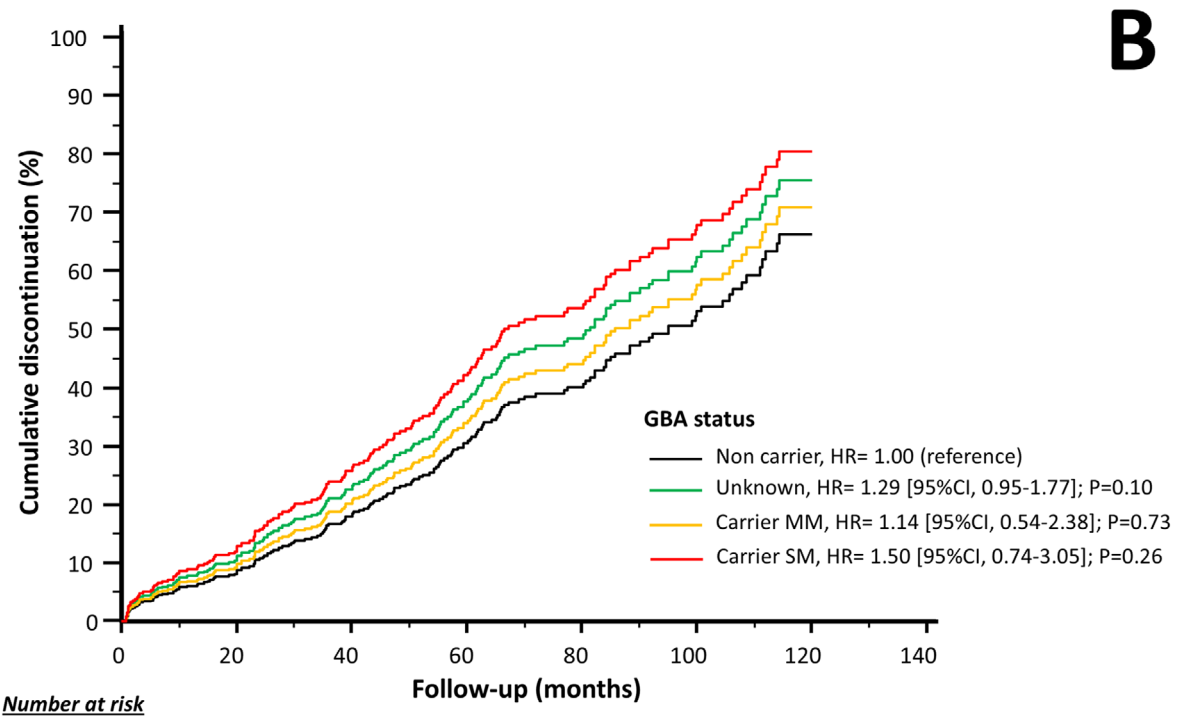


Number at risk

Non carrier	266	191	127	74	44	29	11	0
Carrier	40	27	18	12	10	5	2	0



Number at risk

Non carrier	266	191	127	74	44	29	11	0
Unknown	206	154	120	73	37	18	5	0
Carrier MM	18	13	10	7	6	3	2	0
Carrier SM	22	14	8	5	4	2	0	0

FIGURE 2 | Adjusted cumulative incidence for LCIG discontinuation. We used Kaplan–Meier method, reporting GBA-PD vs. PD noncarriers (panel A) and GBA-PD according to mutations status vs. PD noncarriers (panel B).

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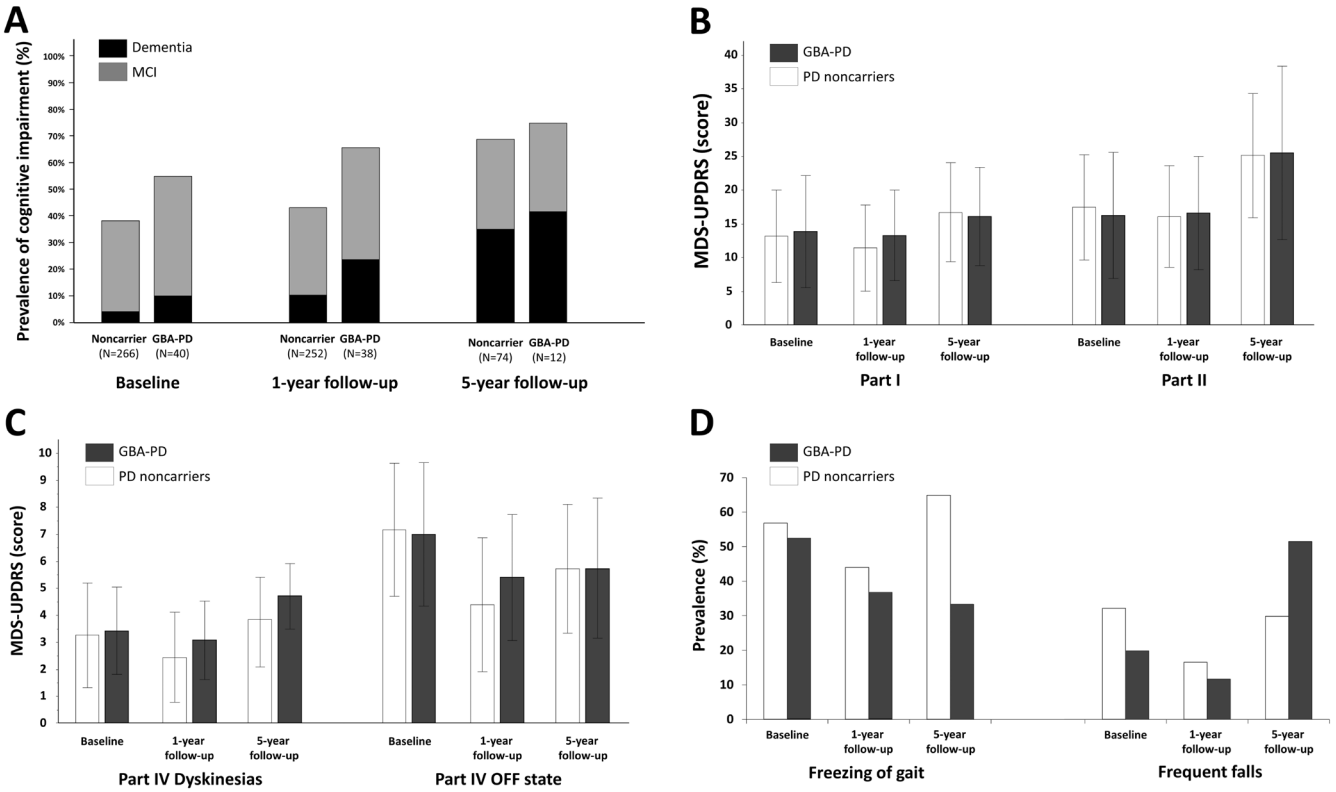

FIGURE 3 | Unadjusted values of selected motor and non-motor symptoms in GBA-PD and PD noncarriers. Prevalence of cognitive impairment (panel A); mean and standard deviation of MDS-UPDRS parts I and II scores (panel B) and part IV subscores related to dyskinesias and OFF-time (panel C) and prevalence of FOG and recurrent falls (panel D).

4.1.2 | Adverse Events

Then, 50.6% of patients reported at least one AE deemed probably related to LCIG treatment and worth being mentioned in medical records. Previous studies on large cohorts of patients on LCIG similarly reported 54% of AEs in a 2-year observation period and 55.1% of AEs during a mean follow-up of 6 years [13, 30]. LCIG-related AEs may occur during the surgical procedure, although the most frequent causes of AEs were device-related, consistent with the established safety profile of LCIG and underlining the importance of careful patient monitoring in the earliest post-LCIG initiation [13, 19, 26]. Taking as established the procedure- and device-related causes of AEs, we focused our safety analysis on potential individual demographic, genetic, and clinical predictors of AEs and found that age, disease duration, motor disability (assessed by HY stage), and comorbidities were independent predictors of AEs, whereas *GBA1* status was not.

4.2 | Efficacy of LCIG

4.2.1 | Levodopa-Responsive Motor Features

In GBA-PD, LCIG led to significant improvement in motor fluctuations and dyskinesias compared to baseline. However, the magnitude of benefit was significantly lower than that observed in PD noncarriers at the 1-year follow-up. These findings suggest that while advanced GBA-PD patients with motor fluctuations and dyskinesias not adequately controlled by oral dopaminergic medications may still benefit from LCIG, their overall outcome may be less satisfactory than that of noncarriers.

Our data from the entire PD cohort confirm that LCIG improves all levodopa-responsive motor symptoms and signs of advanced PD, including motor-related activities of daily living, the quality of ON-state motor performance, motor fluctuations, and dyskinesias, in line with findings from previous open-label studies with medium- and long-term follow-up [12, 13, 19, 20, 31–35]. This effectiveness is accompanied by a simplified therapeutic regimen with oral medications, as reflected by the reduced use of concomitant add-on medications—such as DAs, iMAO-B, iCOMT, and amantadine—at the 1-year follow-up. We additionally observed a reduced frequency of patients presenting with complex/biphasic dyskinesias [36] supporting LCIG's role in streamlining the management of motor complications and improving overall patient outcome [12, 13, 19, 20, 31–35].

4.2.2 | Non-Levodopa-Responsive Motor Features

At the 1-year follow-up, no significant differences were observed in axial symptoms and signs between GBA-PD and noncarriers. Both groups showed similar worsening of the nondopaminergic deficiency score and disease progression, as measured by the HY stage. LCIG significantly improved posture abnormalities, frequent falls, and FOG but provided no benefit on dysphagia or postural instability. These data suggest that LCIG may reduce frequent falls in the short term by improving levodopa-responsive features of gait (e.g., FOG) but has limited impact on

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TABLE 4 | Follow-up clinical data (adjusted change) of the whole study population and by *GBA* status 1 year after LCIG initiation.

Variable (change between T0 and T1)	Total population ($N=481$)	p^f	GBA-PD ($N=38$)	Noncarriers ($N=252$)	p^g for group	p^g interaction group–time
Duration of follow-up on LCIG at T1, months, mean [SD]	12.2 (1.7)	—	12.6 (1.8)	12.2 (1.6)	—	—
MDS-UPDRS score						
Part I, mean [SE]	−0.7 [0.2]	**0.002**	−0.7 [0.8]	−1.2 [0.4]*	0.39	0.57
Part II, mean [SE]	−1.4 [0.3]	**< 0.001**	0.9 [0.9]	−1.9 [0.5]*	0.65	**0.015**
Part III,[a] mean [SE]	−1.7 [0.5]	**< 0.001**	−0.3 [1.6]	−2.5 [0.7]*	0.19	0.23
Part IV (motor complications), mean [SE]	−3.3 [0.2]	**< 0.001**	−2.0 [0.7]*	−3.7 [0.3]*	0.18	**0.035**
Motor complications						
Dyskinesias score[b], mean [SE]	−0.7 [0.1]	**< 0.001**	−0.4 [0.3]*	−0.9 [0.1]*	0.23	0.14
Dyskinesias, *N* (%)	391 (81.3) ↓, $N=50$; ↑, $N=29$	**0.024**	31 (81.6) ↓, $N=5$; ↑, $N=6$	191 (75.8) ↓, $N=26$; ↑, $N=15$	0.070	**0.047**
Complex/diphasic dyskinesias, *N* (%)	55 (11.4) ↓, $N=77$; ↑, $N=18$	**< 0.001**	6 (15.8) ↓, $N=5$; ↑, $N=2$	29 (11.5)* ↓, $N=31$; ↑, $N=9$	0.86	0.32
OFF state[b], mean [SE]	−2.6 [0.1]	**< 0.001**	−1.6 [0.5]*	−2.8 [0.2]*	0.36	**0.036**
OFF state (motor fluctuations), *N* (%)	303 (63.0) ↓, $N=165$; ↑, $N=9$	**< 0.001**	27 (71.1) * ↓, $N=10$; ↑, $N=0$	161 (63.9)* ↓, $N=82$; ↑, $N=6$	0.43	0.66
Dopaminergic deficiency score[c], mean [SE]	−1.8 [0.3]	**< 0.001**	−0.3 [1.0]	−2.3 [0.4]*	0.68	**0.048**
Nondopaminergic deficiency score[c,e], mean [SE]	2.7 [0.2]	**< 0.001**	2.2 [0.7]*	2.3 [0.4]*	0.86	0.97
Hoehn–Yahr stage, mean [SE]	0.0 [0.3]	0.78	−0.1 [0.1]	0.0 [0.4]	0.46	0.31
Non-motor symptoms						
Cognitive impairment[d], *N* (%)	227 (47.2) ↓, $N=18$; ↑, $N=41$	**0.004**	25 (65.8) ↓, $N=2$; ↑, $N=5$	109 (43.3) ↓, $N=11$; ↑, $N=22$	0.65	0.47
MDS-UPDRS—item 1.1, mean [SE]	0.12 [0.03]	**< 0.001**	0.31 [0.11]*	0.04 [0.04]	**< 0.001**	**0.011**
MoCA score ($N=297$)	−1.5 [0.2]	**< 0.001**	−2.2 [0.6]*	−1.2 [0.2]*	**< 0.001**	**0.043**
FAB score ($N=143$)	−0.5 [0.2]	**0.002**	0.4 [0.6]	−0.4 [0.2]	0.050	0.14
Hallucinations and psychosis, *N* (%)	98 (20.4) ↓, $N=49$; ↑, $N=30$	**0.042**	12 (31.6) ↓, $N=7$; ↑, $N=1$	46 (18.3) ↓, $N=29$; ↑, $N=17$	0.33	0.44
MDS-UPDRS—item 1.2, mean [SE]	0.02 [0.03]	0.49	−0.08 [0.11]	0.02 [0.05]	**< 0.001**	0.43
Depression and/or Anxiety, *N* (%)	289 (60.1) ↓, $N=46$; ↑, $N=40$	0.59	26 (68.4) ↓, $N=6$; ↑, $N=5$	142 (56.3) ↓, $N=20$; ↑, $N=19$	0.12	0.89

(Continues)

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TABLE 4 | (Continued)

Variable (change between T0 and T1)	Total population ($N=481$)	p^f	GBA-PD ($N=38$)	Noncarriers ($N=252$)	p^g for group	p^g interaction group–time
MDS-UPDRS—item 1.3 + item 1.4, mean [SE]	−0.25 [0.07]	**< 0.001**	−0.23 [0.24]	−0.37 [0.11]*	0.34	0.62
Impulse control disorders, N (%)	63 (13.1) ↓, $N=56$; ↑, $N=11$	**< 0.001**	7 (18.4)* ↓, $N=7$; ↑, $N=0$	32 (12.7)* ↓, $N=28$; ↑, $N=7$	0.27	0.72
REM sleep behavior disorder, N (%)	185 (38.5) ↓, $N=37$; ↑, $N=25$	0.16	16 (42.1) ↓, $N=3$; ↑, $N=2$	89 (35.3) ↓, $N=23$; ↑, $N=14$	0.96	0.14
Sleep problems MDS-UPDRS—item 1.7, mean [SE]	−0.09 [0.05]	0.09	−0.35 [0.22]	−0.16 [0.07]*	0.94	0.37
Pain MDS-UPDRS—item 1.9 + 4.6, mean [SE]	−0.32 [0.07]	**< 0.001**	−0.46 [0.24]	−0.27 [0.11]*	0.36	0.50
Urinary problems MDS-UPDRS—item 1.10, mean [SE]	0.00 [0.04]	0.94	−0.19 [0.16]	0.01 [0.07]	0.71	0.22
Orthostatic hypotension, N (%)	92 (19.2) ↓, $N=26$; ↑, $N=33$	0.43	8 (21.1) ↓, $N=3$; ↑, $N=4$	38 (15.1) ↓, $N=13$; ↑, $N=11$	0.21	**0.041**
MDS-UPDRS—item 1.12, mean [SE]	−0.04 [0.04]	0.27	0.19 [0.12]	−0.10 [0.06]	0.32	**0.036**
Non-levodopa-responsive symptoms						
Dysphagia, N (%)	66 (13.8) ↓, $N=21$; ↑, $N=25$	0.66	4 (10.5) ↓, $N=0$; ↑, $N=1$	34 (13.5) ↓, $N=14$; ↑, $N=12$	0.26	0.11
MDS-UPDRS—item 2.2 + 2.3, mean [SE]	−0.02 [0.05]	0.75	0.08 [0.13]	−0.12 [0.09]	0.64	0.36
Frequent falls, N (%)	92 (19.2) ↓, $N=94$; ↑, $N=23$	**< 0.001**	5 (13.2) ↓, $N=6$; ↑, $N=2$	47 (18.7)* ↓, $N=55$; ↑, $N=12$	0.69	0.59
MDS-UPDRS—item 2.12, mean [SE]	−0.21 [0.05]	**< 0.001**	−0.08 [0.13]	−0.23 [0.08]*	0.34	0.42
Freezing of gait, N (%)	242 (50.4) ↓, $N=109$; ↑, $N=39$	**< 0.001**	14 (36.8) ↓, $N=10$; ↑, $N=4$	111 (44.0)* ↓, $N=59$; ↑, $N=23$	0.87	0.81
MDS-UPDRS—item 2.13, mean [SE]	−0.37 [0.05]	**< 0.001**	−0.15 [0.13]	−0.40 [0.08]*	0.36	0.22
Postural instability, N (%)	214 (44.5) ↓, $N=55$; ↑, $N=52$	0.85	18 (47.4) ↓, $N=4$; ↑, $N=4$	121 (48.0) ↓, $N=31$; ↑, $N=29$	0.93	0.77
MDS-UPDRS—item 3.12, mean [SE]	−0.03 [0.05]	0.47	0.00 [0.11]	−0.08 [0.08]	0.70	0.66
Posture abnormalities, N (%)	128 (26.7) ↓, $N=54$; ↑, $N=28$	**0.005**	8 (21.1) ↓, $N=6$; ↑, $N=1$	57 (22.6) ↓, $N=26$; ↑, $N=18$	0.38	0.62
MDS-UPDRS—item 3.13, mean [SE]	−0.04 [0.03]	0.26	0.04 [0.10]	−0.04 [0.05]	0.20	0.57
Peripheral neuropathy, N (%)	94 (19.5) ↓, $N=0$; ↑, $N=25$	**< 0.001**	6 (15.8) ↓, $N=0$; ↑, $N=1$	34 (13.5) ↓, $N=0$; ↑, $N=6$	0.99	0.51
Dopaminergic medications						

(Continues)

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TABLE 4 | (Continued)

Variable (change between T0 and T1)	Total population ($N=481$)	p^f	GBA-PD ($N=38$)	Noncarriers ($N=252$)	p^g for group	p^g interaction group–time
Oral levodopa dose (mg/day), mean [SE]	−644 [20]	**< 0.001**	−664 [60]*	−609 [29]*	0.99	0.48
Concomitant DA, N (%)	205 (42.7) ↓, $N=131$; ↑, $N=20$	**< 0.001**	15 (39.5)* ↓, $N=10$; ↑, $N=1$	109 (43.3)* ↓, $N=72$; ↑, $N=15$	0.62	0.22
LED from DA (mg/day), mean [SE]	−69 [8]	**< 0.001**	−68 [28]*	−60 [11]*	0.65	0.78
Concomitant MAO-B inhibitors, N (%)	51 (10.6) ↓, $N=129$; ↑, $N=16$	**< 0.001**	5 (13.2) ↓, $N=9$; ↑, $N=2$	34 (13.5)* ↓, $N=72$; ↑, $N=10$	0.95	0.38
Concomitant COMT inhibitors, N (%)	46 (9.6) ↓, $N=144$; ↑, $N=12$	**< 0.001**	5 (13.2)* ↓, $N=12$; ↑, $N=3$	28 (11.1)* ↓, $N=74$; ↑, $N=4$	0.79	0.32
LED from LCIG, mean [SD]	1337 [429]	—	1351 [531]	1319 [444]	0.054	—
Total-LED (mg/day), mean [SE]	456 [27]	**< 0.001**	443 [104]*	485 [40]*	0.69	0.70
Nondopaminergic medications						
Amantadine, N (%)	41 (8.5) ↓, $N=52$; ↑, $N=12$	**< 0.001**	5 (13.2)* ↓, $N=6$; ↑, $N=0$	18 (7.1)* ↓, $N=29$; ↑, $N=4$	0.57	0.65
Anticholinergics, N (%)	14 (2.9) ↓, $N=9$; ↑, $N=7$	0.80	0 (0.0) ↓, $N=0$; ↑, $N=0$	9 (3.6) ↓, $N=5$; ↑, $N=6$	0.42	0.74
Antidepressants, N (%)	183 (38) ↓, $N=29$; ↑, $N=51$	**0.018**	22 (57.9) ↓, $N=2$; ↑, $N=9$	101 (40.1) ↓, $N=17$; ↑, $N=31$	0.16	0.21
Antipsychotics, N (%)	117 (24.3) ↓, $N=16$; ↑, $N=40$	**0.002**	16 (42.1) ↓, $N=0$; ↑, $N=1$	59 (23.4) ↓, $N=11$; ↑, $N=25$	0.13	0.092
Antidementia, N (%)	16 (3.3) ↓, $N=5$; ↑, $N=5$	0.99	3 (7.9) ↓, $N=1$; ↑, $N=1$	9 (3.6) ↓, $N=4$; ↑, $N=2$	0.52	0.33
Anti-orthostatic hypotension, N (%)	22 (4.6) ↓, $N=6$; ↑, $N=11$	0.33	5 (13.2) ↓, $N=0$; ↑, $N=2$	9 (3.6) ↓, $N=2$; ↑, $N=6$	0.52	0.37

Abbreviations: COMT, catechol-O-methyltransferase; DA, dopamine agonists; iMAO-B, MonoAmine Oxidase type B Inhibitors; IR, levodopa immediate release; LED, levodopa equivalent dose; MDS-UPDRS, International Parkinson and Movement Disorders Society Unified Parkinson's Disease Rating Scale; SD, standard deviation.

[a]In "ON" condition.

[b]Dyskinesia is defined as the sum of MDS-UPDRS III items 4.1 + 4.2, whereas OFF is the sum of items 4.3 + 4.4 + 4.5 + 4.6.

[c]Calculated motor examination scores as proposed by Levy et al. [Supplementary Reference 4 in Appendix S1].

[d]Diagnosis of mild cognitive impairment or dementia [Supplementary References 2 and 3 in Appendix S1, respectively].

[e]MDS-UPDRS—item 2.9 + 2.11–2.13 + 3.9–3.13.

[f]According to the mixed model for repeated measures (linear or logistic) adjusted for sex, age, and disease duration at LCIG initiation, sex, duration of follow-up, and—only for continuous variables—the baseline value of each parameter.

[g]According to the mixed model for repeated measures (linear or logistic) adjusted for sex, age, and disease duration at LCIG initiation, sex, duration of follow-up, and—only for continuous variables—the baseline value of each parameter with and without testing also for the interaction between time and GBA status (carriers vs. non-carriers); p-values are provided for between-group differences (first column) and for time–group interaction (second column).

*Statistically significant within-group difference (T1 vs. T0; according to Student's t test for paired data [continuous variables] or McNemar's test [categorical variables] as appropriate).

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levodopa-resistant axial complications. This aligns with the notion that LCIG may benefit not only axial levodopa-responsive gait and balance issues [13, 32, 37, 38], but also features usually considered unresponsive to optimized oral therapy, such as posture abnormalities, falls, and FOG [38–42]. At the 5-year follow-up, axial complications worsened in both groups without major differences, except for a significant group–time interaction for frequent falls, which were more frequent in GBA-PD than in noncarriers. In a previous study, GBA-PD had a higher risk of progressing to postural instability and reaching HY stage 3 within 15years of diagnosis compared to noncarriers [17]. This discrepancy is likely due to differences in disease duration at baseline: Stoker et al. began their observation at the time of first diagnosis in two community-based incident PD cohorts [17], whereas our observation period started in patients with advanced PD, with an average disease duration of 13years at baseline.

4.2.3 | Non-Motor Symptoms

Global and frontal-lobe cognitive functions, along with MoCA and FAB scores, declined in the entire cohort at both the 1- and 5-year follow-up visits. However, the rate of decline was significantly faster in GBA-PD patients than in noncarriers. The worse baseline cognitive scores of GBA-PD and their more rapid progression of cognitive decline over time compared to noncarriers are consistent with the known *GBA*-related phenotype [4–6, 17, 22]. We emphasize that about 40% of patients already had cognitive impairment-ranging from MCI to moderate dementia-at the time of LCIG initiation. This supports the notion that levodopa infusion is a suitable first-line therapeutic option in advanced PD patients with signs of mild-to-moderate cognitive decline, whereas STN-DBS is the preferred option in patients with preserved cognitive functions [4, 13]. In contrast, neuropsychiatric symptoms (i.e., hallucinations, psychosis, ICDs, depression, and anxiety) improved at 1year after LCIG initiation [13, 33]. This improvement is likely due to the reduction or discontinuation of add-on therapies, such as DAs and/or amantadine, which are known to exacerbate these symptoms. Notably, this improvement was more pronounced in GBA-PD than in noncarriers, suggesting that levodopa infusion may be a safe option for advanced GBA-PD with these neuropsychiatric issues [3, 5]. Finally, OH symptoms worsened more in GBA-PD patients than in noncarriers at both the 1- and 5-year follow-up, reflecting the greater burden of autonomic dysfunction in carriers of pathogenic *GBA1* gene variants [3, 5, 10, 43].

4.3 | Limitations and Strengths

There are limitations to acknowledge. This was not a prospective controlled clinical trial, and the retrospective nature of the study intrinsically resulted in missing data, particularly regarding AEs reporting, which was likely limited to events deemed reasonably related to treatment. Concerning efficacy, it is unlikely that this design played a confounding effect on the results because all analyses were adjusted for several potential confounders, such as sex, age, and disease duration at LCIG initiation, duration of follow-up, and the baseline value of each parameter. Prospective pragmatic real-world trials on large cohorts of advanced PD patients treated with levodopa infusion therapies are warranted to replicate our results, including objective criteria for AE coding using validated tools, such as the Medical Dictionary for Regulatory Activities.

On the other hand, this design may also be considered a major strength of the study as it allowed us to collect "real-world" clinical data on LCIG treatment over an observation period ranging up to 10years on consecutive patients that is relatively less biased than the data obtained from more homogeneous but selected cohorts reported in randomized clinical trials. Our safety analysis included all consecutive patients who initiated LCIG treatment at both secondary and tertiary referral centers, making our results representative of the broader LCIG-treated population, with AE rates comparable to those reported in the largest studies available so far [13, 19, 20]. The major strength of this study is being the first to focus on *GBA1* mutation status as a potential modifier of clinical outcome over both short- and long-term follow-up. The large nationwide population of 512 patients recruited by neurologists with heterogeneous prescription patterns from most major movement disorders clinics throughout Italy further supports the external validity of the findings.

5 | Conclusions

This long-term "real-world" study confirms the sustained effectiveness of LCIG in reducing motor fluctuation and dyskinesias, as well as improving both motor and non-motor experiences of daily living in a large cohort of advanced PD patients. *GBA1* mutations did not detrimentally impact the long-term safety profile of LCIG. LCIG is a safe and effective treatment option in advanced GBA-PD patients, including those with cognitive decline at baseline. Nonetheless, the magnitude of benefit on motor disability and complications was lower, and cognitive deterioration progressed more rapidly in carriers than noncarriers.

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Ethics Statement

The authors confirm that they have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines. Ethics Committee of the coordinating center: Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano; reference number: CE n.32/2023. Concerning the PARKNET consortium: Project code: PARK-Net 3-22033-ID 3951. The study was approved by the ethics committee of each participating center and conducted in accordance with the declaration of Helsinki, including written informed consent to the use of patient anonymized clinical data for research purposes according to local regulatory requirements.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

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