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ORIGINAL ARTICLE

Clinical and pharmacokinetics equivalence of multiple doses of levodopa benserazide generic formulation *vs* the originator (Madopar)

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Aims: While several generic preparations of levodopa/carbidopa and levodopa/benserazide (LBD) are currently available, pharmacokinetic (PK) equivalence and therapeutic equivalence studies with levodopa generics are not available in Italy. Lack of data on generic formulations is a critical factor for their limited use in this country and often lead patients to refuse the generic version of the branded drug.

Methods: An experimental, 2-centre, randomized, double-blind, 2-sequence, noninferiority cross-over study was designed to evaluate both the PK equivalence and clinical equivalence of multiple doses of the *generic* preparation of LDB, Teva Italia, compared to the *originator* (Madopar). Forty-three out-patients with a diagnosis of idiopathic Parkinson's disease on LDB, were recruited and randomly assigned to 1 of 2 study sequences: generic–originator or originator–generic. Clinical evaluations were performed at the end of each study period. A PK study with an LDB fixed dose (100 + 25 mg) was performed in a subpopulation of 14 subjects.

Results: Clinical data showed a reduction of 0.49 and 1.54 in the mean UPDRS III scores for the LDB and the originator, respectively. The 95% CIs [−2.21: 0.11] of the mean difference original *vs* LDB are smaller than the clinically significant difference of 3 UPDRS III points, supporting the conclusion that the treatment with LDB is not inferior to the originator. No statistically significant differences were found with respect to area under the curve to last dose, half-life, maximum concentration, time to maximum concentration and last observed concentration.

Conclusion: These findings prove the therapeutic clinical equivalence as well the PK equivalence of the *generic* LDB and the *originator* (Madopar).

KEYWORDS

generic formulation, noninferiority, originator, pharmacokinetic equivalence

The authors confirm that the Principal Investigator for this paper is Fabrizio Stocchi and that he had direct clinical responsibility for patients.

1 | INTRODUCTION

Levodopa (LD) in combination with peripheral dopa decarboxilase inhibitors (carbidopa, benserazide) still offers the best symptomatic control of Parkinson's disease (PD). All patients require such a drug during the course of their disease. LD provides the most effective symptomatic control of motor symptoms in almost the totality of PD patients[1,2] and, since its introduction, has dramatically improved survival and quality of life for people with PD.[3] In the early stage of the disease patients treated with LD return to their normal functionality. However, dyskinesia and on–off fluctuations develop in about 30% of patients within 2.5 years and in virtually all PD patients after 10 years.[4,5] Many studies on PD patients with motor fluctuations, showed a strict correlation between LD pharmacokinetics (PK) and clinical response.[6-10] The clinical adjustment of LD dose is crucial in the treatment of PD patients and conceivably changes in PK characteristics of the drugs may result in an abrupt change of patient's clinical response.[11] All studies exploring the relationship between LD PK and its clinical effect had been conducted with *originator* drugs whereas generic preparations of LD have been tested on healthy volunteers only. LD PK significantly differs between normal subjects and PD patients.[12] Moreover, in normal volunteers it is not possible to evaluate the clinical response to the drug. Today several generic preparations of LD/carbidopa and LD/benserazide (LDB) are available but data on both clinical and PK equivalence with LD generics are not. LD preparations might differ from the *originator* for bioavailability or different PK characteristics which may induce unpredictable off periods and worsening of dyskinesia. PK and therapeutic equivalence studies with generic formulation of LD are lacking. It is of a paramount importance to increase knowledge about both LD generic preparation and related patients' clinical response to tailor made their use in PD.

What is already known about this subject

- Levodopa generic preparations may differ from the originator for bioavailability or different pharmacokinetic characteristics. These differences may induce a sudden and significant worsening of parkinsonian symptoms. Therefore, it is of a paramount importance to clarify pharmacological characteristics of generics drugs and patients' clinical response to them in order to optimize their use.

What this study adds

- With this study we demonstrated the pharmacokinetic equivalence and the therapeutic clinical equivalence of a generic formulation of levodopa/benserazide with its *originator* in a cohort of advanced parkinsonian patients. The results of this study will increase knowledge about generic formulations of levodopa and patients' clinical response to these drugs and will encourage their acceptance by both patients and physicians.

2 | METHODS

This study was conducted at the Institute for Research and Medical Care San Raffaele Pisana in Rome, and at the University *G. D'Annunzio* of Chieti, Department of Neurology, Italy, after approval by the local institutional IRBs/IECs. The trial was conducted according to the provisions of the Declaration of Helsinki (Oct 1996) and to the International Conference on Harmonisation (ICH) Guidelines on GCP (CPMP 135/95). This trial was funded by AIFA (Call 2009 for Independent Research Projects on Drugs).

The study has been registered on clinicaltrials.gov. NCT 02741947.

2.1 | Patients

Eligible patients were recruited from the 2 hospitals' out-patient clinics. Written consent was obtained from each subject at screening visit and before performing any study procedures. Inclusion criteria were diagnosis of idiopathic PD, age 30–75 years, moderate to advanced stages of the disease, stable dosage of LDB for at least 4 months and a good response to LD (i.e. $\geq$ 30% improvement in the Unified PD rating scale [UPDRS] score), at least 2 hours *off time* per day during waking hours on Houser Home Diary. Subjects with very severe motor fluctuations and/or dyskinesia as well as subjects receiving catechol-o-methyltransferase inhibitors were excluded from enrolment.

2.2 | Study design

The trial was an experimental 2-centre, randomized, double-blind, 2-sequence, noninferiority cross-over study. Subjects who agreed to participate in the study needed to be on stable dosage of all anti-PD agents for at least weeks prior to study entry. Patients who changed treatment regimen <4 weeks prior to screening, need to wait an interval of 4 weeks (run-in) prior to begin the first treatment period. This run-in period was performed only at the beginning of the study in order to stabilize LD dosages and did not serve as a wash-out period; therefore, it was not repeated between the 2 treatment periods. The study contemplated 2 treatment periods of 4 weeks each (t_0–t_1 and t_1–t_2); at the end of the first treatment period patients in each formulation group underwent an overnight switch to the same dose of the alternative formulation (t_1–t_2; Figure S1: flowchart). The formulations of LD allowed in the trial were: Madopar 100 + 25 and Madopar 200 + 50 (1/2 or 1 tablet) taken 4 or 5 times a day. Each study capsule (see blinding procedures) contained 100 mg of LDB, therefore subjects enrolled needed to take 1 or 2 capsules at each administration time depending on their regimen schedule at the time of baseline. The LD dose was kept stable during the whole duration of trial. Baseline evaluations were performed at the beginning of the first treatment period while efficacy assessments were repeated at the end of each study

period and included: UPDRS, part I-II-III-IV; Hoehn–Yahr stage; Schwab–England activities of daily living scale; Clinical Global Impression—Improvement (CGI-I) and a questionnaire to express preference between the 2 treatments.

2.3 | Randomization and blinding procedures

The random allocation of patients to 1 of the 2 treatment groups (generic-originator, originator-generic) was performed at the end of the run-in period and was managed centrally, according to an automatically generated randomization list by an allocation ratio of 1:1. For each randomization number, a sealed envelope containing the randomization code was prepared by the data manager who generated the randomization list.

Mechanical blinding (encapsulation) was used to ensure the double-blind nature of the study. Because patients enrolled in the trial received different doses of LDB, the study planned an over-encapsulation of 100 mg dosage in size 00 gelatine capsules, so the blind was kept for all doses. Capsules were then placed in a narrow opaque bottle and labelled as *Treatment A* and *Treatment B* before administration to the patient. Study drug was handed out to subjects at the beginning of each maintenance period. Subjects and investigators were kept blinded, while the site pharmacist and the nurse who administered study medication were not blind throughout this part of the study.

2.4 | Study endpoints

This was a noninferiority study aimed to investigate both, the clinical equivalence, and the PK profile of the *generic* LDB preparation compared to the *originator* (Madopar) in patients with PD.

The objective of the study was considered met if noninferiority was demonstrated in improving motor symptoms as well as the equivalence by the total area under the curve (AUC) of the generic LDB compared with originator. The noninferiority hypothesis of LDB clinical efficacy was evaluated by the UPDRS part III (total motor score). The equivalence was assessed with the LD PK study taking the total AUC to last dose (AUC_{0-t}) and to infinity (AUC_{0-inf}) and the maximum concentration (C_{max}) as primary parameters.

The secondary clinical objective was the comparison of the proportion of patients with a score of 1 or 2 (*very much improved* or *much improved*) on the CGI-I scale in the 2 treatments. Secondary PK endpoints were the demonstration of PK equivalence in the following parameters: last observed concentration, C_{max}, time to maximum concentration (T_{max}) and the half-life after the last dose. Safety was evaluated by recording any treatment associated adverse event (AE) reported from screening to the end of treatment.

2.5 | PK analysis

A PK study with a fixed dose (100 + 25 mg) was performed in a subpopulation of 14 subjects selected from the Institute for Research and Medical Care San Raffaele Pisana. Subpopulation was selected among the 24 subjects taking LDB 100/25 mg as first LD morning dose: out of those, only 14 decided to sign the PK consent form and could therefore being enrolled into the PK substudy.

A single dose of LDB (100/25 mg of originator or generic) was administered orally after an overnight fast. A light breakfast was allowed after the onset of the drug benefit, but not before 2 hours since dose administration. To avoid repeated venepuncture, a peripheral venous cannula was placed in the forearm vein. All anti-PD medications were withheld for the total length of PK analysis.

PK parameters for LD were calculated from blood samples taken immediately before intake (predose) and at regular intervals (15, 30, 45, 60, 75, 90, 120, 150, 180, 210, 260 and 360 minutes postdose) after single administration at the end of each study period.

Blood samples were collected in sodium heparin Vacutainers and plasma was obtained immediately by cooled centrifugation at 704× g for 10 minutes. Plasma samples were stored at −80° C for 2 weeks until analysis. The laboratory technician was blinded to treatment sequence. All samples were processed using the Chromsystem's commercial kit for the in vitro diagnosis of plasmatic human catecholamines (Chromsystems GmbH, Germany) according to the manufacturer's instructions, with the LD/DHPG/DOPAC (3,4 Dihydroxyphenylglycol; 4-dihydroxybenzylamine) modified mobile phase for the L-DOPA analysis. The kit was run on a PerkinElmer's Series 200 high-performance liquid chromatography apparatus (Perkin-Elmer, USA) using a Chromsystem's CLC100 Elettochemical detector (Chromsystems GmbH) equipped with a carbon glass electrode (work electrode) and a potassium chloride electrode (reference electrode). Particularly, the analysis was performed by extracting 0.05 mL of sample spiked with 3,4-dihydroxybenzylamine as internal standard before any extraction procedure. The data were processed using Total Chrome software (PerkinElmer). The recovery of the methods was 83%; the limit of detection and the limit of quantitation assessed in our conditions were 2.5 ng/mL and 8.0 ng/mL, respectively; the linearity ranged between 10 and 1000 ng/mL, the accuracy between 2.7 and 4.2% and precision (coefficient of variation) between 3.7% and 5.1%.

2.6 | Statistical methodology

The sample size calculation was based on the clinical primary endpoint, on data generated by the historical series of PD patients treated in the coordinating centre of San Raffaele Pisana. Assuming a difference in the UPDRS motor score of 3 (as explained below) between both treatments as clinically relevant, and further assuming a SD of 3.96, 39 patients were necessary to achieve 90% power (simplified calculation as 2-sided *t* test for paired samples; $\alpha = 5\%$). Anticipating a 15% drop-out, we planned to recruit 44 patients.

The presence of significant differences in clinical and demographics characteristics between treatment sequence and recruiting clinical centre was tested with the Student *t* test and the χ^2 test for continuous and categorical variables, respectively. Regarding the

primary clinical endpoint, it was assessed a difference of 3 points on the UPDRS motor score as the margin for noninferiority. This cut-off value was set according to previous clinical trials with dopaminergic medications, which reported UPDRS III improvements below 5 points as not clinically meaningful, since they did not correspond to changes in activities of daily living (UPDRS part II) or improvement in the CGI-I.[13,14] Other trials reported smaller values,[15] and therefore we decided to observe a more conservative criterion, setting the limit of clinical significance to a value of 3 points of the UPDRS motor score.

The presence of a carryover effect was tested comparing the sum of the values measured in the 2 periods for each subject across the 2 sequence groups by means of the Student *t* test for independent samples.[16] In addition, the treatment effects in each sequence was visualized using plots separately for both sequences and stratified for clinical centre. Individual variability in the 2 sequences was evaluated comparing the average value of individual coefficient of variation for all subjects, i.e. intraindividual coefficient of variation.

A Student *t* test was applied to evaluate the difference between treatment effect on the UPDRS III as compared with the baseline value. Drop out individuals were explored to check if any pattern could be associated to treatment group, clinical centre, duration of PD, UPDRS at baseline, sex or age. To take into account the presence of confounding and to test for interaction we modelled a maximum likelihood (ML) estimation which included fixed-effects and random-effects terms in the likelihood function. The final model tested the *treatment*period* interaction to assess in a multivariate setting the presence of carry-over effect. Sequence of treatment, clinical centre, duration of PD, UPDRS at baseline, sex, age, body mass index, dose of standard treatment with LD, Hoehn–Yahr stage and Schwab–England activities of daily living scale were tested as potential confounders in the regression model.

As regards to the secondary objective related to proportion of patients with a score of 1 or 2 (*very much improved* or *much improved*) on the CGI-I scale, this endpoint could not be properly evaluated, since only 2 patients reported a score of 1 or 2 (one in the group starting with the LDB, the other in those starting with the originator). We therefore compared for descriptive purposes only mean CGI-I value obtained in the 2 groups at the end of each treatment period.

Regarding the PK study, 12 patients were considered a statistical meaningful sample size for a PK equivalence study according to the DOC generics document registered by the Italian Ministry of Health on 1 October 2003.[17]

PK parameters were estimated by noncompartmental analysis and shown as geometric mean and range for the lognormally distributed variables (AUC_{0-t}, AUC_{0-inf}, C_{max}, half-life, last observed concentration), or median and range for non-normally distributed variables (T_{max}). For log normal variables, range was computed dividing (lower range) or multiplying (upper range) the geometric mean by the geometric standard deviation; for non-normal variables the range was represented by the first (lower range) and third (upper range) quartiles.

The difference between the 14 pairs of samples was assessed by means of paired *t* test, or alternatively by Wilcoxon signed rank test where appropriate. Alongside, the PK equivalence for AUC_{0-t}, AUC_{0-inf} and C_{max} was assessed by means of the Anderson and Hauck method,[18,19] using the 90% confidence interval (CI) with respect to an equivalence range of 80–125% according to the ANMAT criteria for bioequivalence.[20] All analyses were implemented in STATA/SE Release 12 for Windows (StataCorp LP, College Station, Texas, USA).

3 | RESULTS

3.1 | Patients

A total of 43 subjects were screened from April 2014 and October 2015; 1 was classified a screening failure, 5 discontinued at the end of the first study period (3 due to AE and 2 due to difficulty in swallowing study capsules) and 37 completed the study. Fourteen subjects agreed to participate in the PK study. The total length of the study was 8 weeks for each subject (plus a 4-week run/in period for those patients not on stable doses of LD).

Forty-two subjects were randomized to 1 of the 2 treatment sequences. The 2 clinical centres of IRCCS San Raffaele Pisana in Rome and the University G. D'Annunzio in Chieti enrolled 33 and 9 patients, respectively (the distribution of patients' characteristics by clinical centre is reported in the Table S1). Patients randomized to the 2 sequences were comparable for demographics and clinical characteristics including the primary key endpoint (UPDRS part III), while patients from the University G. D'Annunzio of Chieti were in general younger and reported lower values of UPDRS (Table S2). Patient characteristics of the whole study group at baseline are reported in Table 1. Compliance was above 90% in each of the treatment groups.

3.2 | Efficacy results and statistical issues

The key objective of the study was to demonstrate noninferiority (therapeutic equivalence) in improving motor symptoms of the *generic* LDB preparation (Teva Italia) compared to the *originator* (Madopar) in patients with PD. Mean values of UPDRS III in the 2 sequences are reported in the Table 2, while Table 3 reports the mean motor improvement including the overall difference between the 2 sequences.

The mean motor symptoms improvement from baseline in patients treated with the generic drug measured as UPDRS part III score was 1.05 points lower than in patients treated with the originator (95% CI -2.21:0.11). No statistically significant difference was found between the 2 treatments, and the lower limit of the 95% confidence interval did not exceed the noninferiority margin set at 3 points of the UPDRS part III score as reported in the methods. All results reported in Table 3 have been evaluated in those patients who contributed data in both treatment periods (n. 37). No significant differences were found when UPDRS III values of patients dropping out have been considered (Table 2 compared to Table S3). Intraindividual variability did not differ between the 2 sequences.

Although ML modelling did not reveal any statistical differences between clinical centres ($\beta = -1.261$, SE = 1.731 $P < .466$), a stratified

TABLE 1 Comparison of main patients' characteristics at baseline (n = 42)

Characteristics, units	Mean ± SD* (%)‡
Treatment sequence	
Originator–generic	20 (47.6%)
Generic–originator	22 (52.4%)
Clinical centre	
IRCCS San Raffaele Pisana (Rome)	33 (78.6%)
University G. D'Annunzio (Chieti)	9 (21.4%)
Male, %	25 (59.5%)
Age, y	67.36 ± 7.87
PD duration, y	5.05 ± 2.69
LD, mg	423.80 ± 130.31
BMI, kg/m^2	27.55 ± 3.85
H&Y score	2.28 ± 0.42
S&E score	86.43 ± 9.06
UPDRS part I, score	1.79 ± 1.57
UPDRS part II, score	8.57 ± 4.75
UPDRS part III, score	18.90 ± 6.00
UPDRS part IV, score	1.71 ± 2.16
UPDRS TOTAL, score	30.93 ± 11.85

*mean ± standard deviation for quantitative variables;

‡percent for qualitative variables; BMI, body mass index; PD: Parkinson's disease; LD: Levodopa; H&Y: Hoehn–Yahr stage; S&E: Schwab–England activities of daily living scale; UPDRS: Unified PD rating scale.

TABLE 2 Descriptive analysis of mean Unified Parkinson's disease rating scale part III scores in the 2 treatment groups at baseline (t_0), and at the end of the 2 study periods (t_1, t_2), respectively

Originator	Generic
*t_0 (n = 20) 19.25 ± 6.34	**t_0 (n = 22) 18.59 ± 5.80
t_1 (n = 18) 17.50 ± 5.93	t_1 (n = 21) 18.47 ± 6.19
t_2 (n = 21) 17.52 ± 6.58	t_2 (n = 16) 18.63 ± 7.81

*SD, standard deviation.

*Baseline value for those patients starting with the originator.

**Baseline value for those patients starting with the Generic.

visual analysis comparing the treatment effect by clinical centre is reported in the Figure S2. The effect of the originator seems more evident in the centre of Chieti, but the small number of patients in this subgroup (7) may account for a large interindividual variability. The inclusion into ML modelling of additional covariates that may have potentially influenced the response to treatment, such as age (β = 0.126, SE = 0.0725 P < .083), sex (β = 0.349, SE = 1.081 P < .746), and duration of PD (β = 0.395, SE = 0.218 P < .07), besides the adjustment for baseline UPDRS part III score (β = −0.967, SE = 0.966 P < .317), reduced the observed difference between sequences, and confirmed the noninferiority hypothesis of the treatment with the generic drug, with a variability of the effect estimated

TABLE 3 Changes in mean Unified Parkinson's disease rating scale part III scores difference (originator *vs* generic treatment; n = 37)

Group	Mean ± SD	SE mean	%iCV	95% CI of the difference
Originator	−1.54 ± 3.11	0.51	9.58%	−2.57; − 0.50
Generic	−0.49 ± 3.67	0.60	10.12%	−1.71; 0.74
Difference (originator – generic)	−1.05 ± 3.48	0.57		−2.21; 0.11

SD, standard deviation; SE; standard error; CI, confidence interval; %iCV-intraindividual coefficient of variation. A difference of 3 points on the Unified Parkinson's Disease rating scale motor score was set as the margin for noninferiority.

well within the threshold considered clinically significant for UPDRS part III (β = −0.240; 95% CI −1.963 to 2.337). The nonsignificant interaction term between treatment and period confirmed that—within the limitation of the study—the analysis was not affected by a carryover effect.

As regards the secondary endpoint related to the CGI-I scale, mean CGI-I values obtained in the 2 groups at the end of each treatment period did not significantly differ, remaining by large in the no-change area represented by a score of 4, as reported in Table 4.

3.3 | PK of LD

The branded (originator) and generic drugs were compared with respect to main PK parameters by the analysis of 14 individuals (11 males, 3 females), as it is graphically displayed in Figure 1 and summarized in Table 5. The PK profile of the 2 compounds is shown in Figure 2.

The PK analysis showed that the 2 formulations are equivalent as measured by AUC_{0-t}, AUC_{0-inf} and C_{max}, in that the 90% CI for generic-to-originator ratio did not exceed the equivalence range of 80–125%. Results are shown in Table 6.

3.4 | Safety

During the study, the occurrence of AEs was continuously monitored. Trial site personnel reported any AE, whether observed by the investigator or reported by the subject. For each suspected AE, the date of onset, the severity, the relation with study drug and period of treatment, the discontinuation date, and the action taken were registered.

TABLE 4 Descriptive analysis of mean Clinical Global Impression—Improvement scores in the 2 treatment groups at the end of the 2 study periods (t_1, t_2) respectively

Originator	Generic
t_1 (n = 18) 4.06 ± 0.80	t_1 (n = 21) 4.30 ± 0.85
t_2 (n = 21) 4.30 ± 0.79	t_2 (n = 16) 3.90 ± 1.06

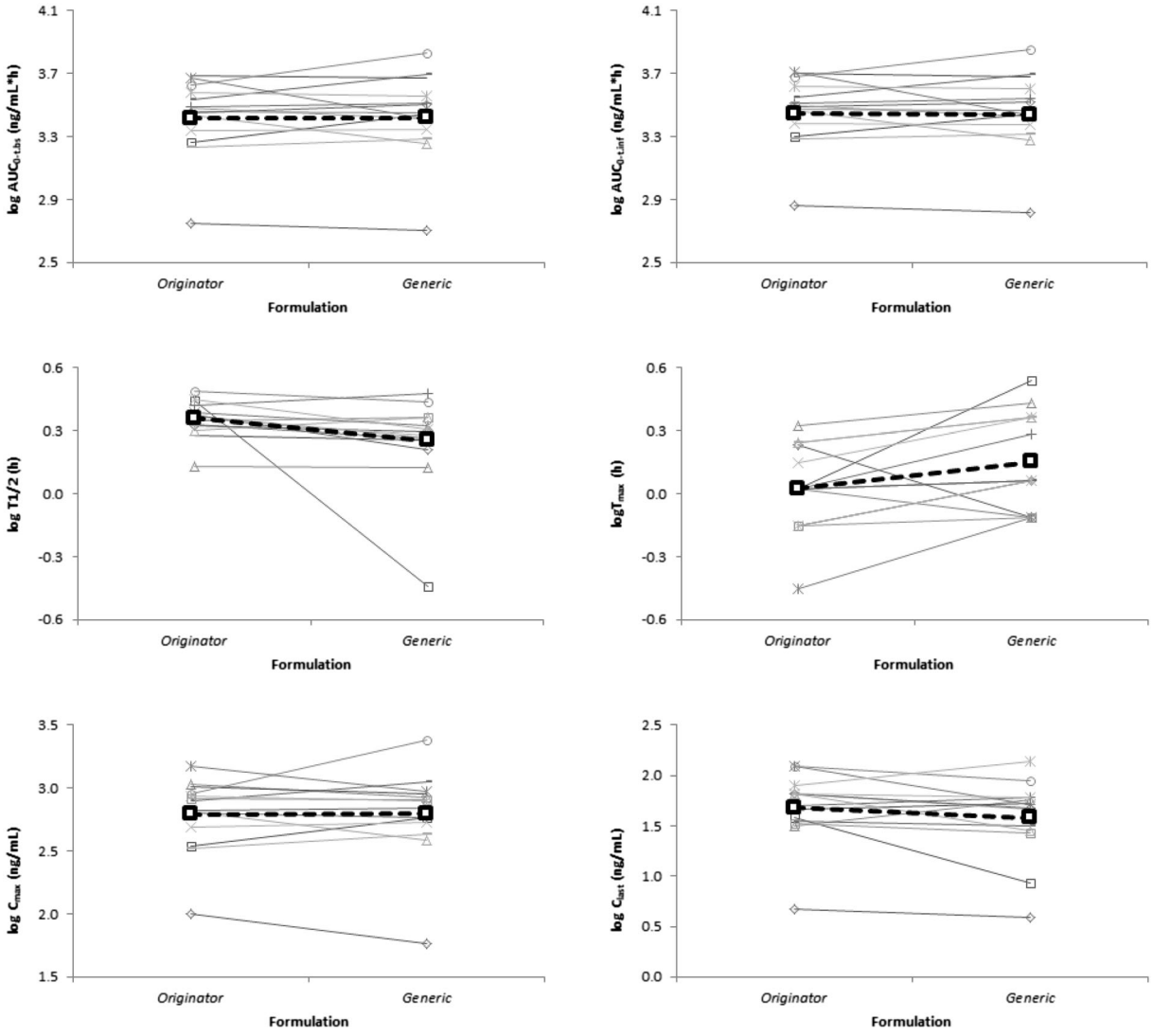

FIGURE 1 Secondary pharmacokinetic endpoints: (a) AUC_{0-t}; (b) AUC_{0-t}; (c)$T_{1/2}$; (d) T_{max}; (e) C_{max}; (f) C_{last}. Dataset comprised 14 pairs: Trend of paired data; the thick bordered indicator (□) shows the geometric mean for the endpoint in each group as it is summarized in Table 5

TABLE 5 Summary of pharmacokinetic parameters with respect to the *originator* and *generic* drug formulations

Pharmacokinetic parameters						
	AUC_{0-t} (ng/mL*h)	AUC_{0-inf} (ng/mL*h)	T1/2 (h)	C_{max} (ng/mL)	C_{last} (ng/mL)	T_{max} (hr)
Originator* (*n*; %CV)**	2603.2 (14; 24.3)	2784.7 (14; 22.1)	2.28 (14; 12.8)	620.2 (14; 29.8)	48.1 (14; 35.8)	1.06 (14; 21.1)
Generic* (*n*; %CV)**	2625.9 (14; 26.8)	2753.7 (14; 24.6)	1.79 (14; 22.1)	627.5 (14; 36.7)	37.8 (14; 36.5)	1.42 (14; 23.4)

AUC_{0-inf}, Total Area Under the Curve to infinity; AUC_{0-t}, Total Area Under the Curve to last dose; C_{max}, Maximum concentration; C_{last}, Last observed concentration; T_{max}, Time to maximum concentration.

*: the geometric mean is shown. **: coefficient of variation in % estimated by 100*log(x) according to Lewontin's formula (Syst Zool 1964,15(2):141–2).

Most AEs occurred during the trial affected the gastrointestinal tract. Two cases of nausea (1 mild and 1 moderate in intensity) and 1 of dyspepsia (moderate) occurred. Two case of diarrhoea were registered, 1 mild in severity that did not interfere with treatment and allowed subject to continue into the study, and 1 moderate in severity that led to study discontinuation. One case of hypotension and 1 case of asthenia were also reported. Vital signs and body weight were measured at each study visit. No significant changes in any of these parameters were noted during the whole length of the trial and for the totality of patients enrolled. Overall, 9 AEs were reported during the study periods, affecting 7 patients. The proportion of patients suffering of AEs was 16.7% (18.9% considering per protocol population). AEs occurred 6 times among patients taking the originator, and 3 times among those on generic drug. The proportion were 28.5 and 18.7%,

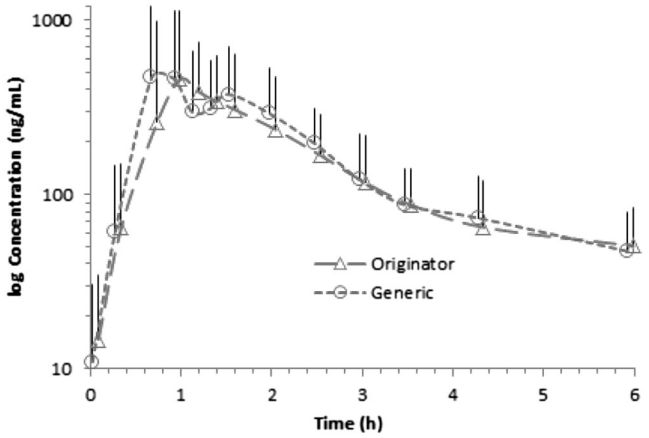

FIGURE 2 Levodopa concentration–time (0.5–6 hours) semilogarithmic plot after administration of single oral doses of originator (levodopa/benserazide 100/25 mg tablets) and after the generic formulation. Time-points and bars represent the average of 14 individuals and the standard deviation, respectively

TABLE 6 Summary of equivalence between pharmacokinetic parameters of *originator* and *generic* drug formulations

Equivalence of pharmacokinetic parameters		
	Generic-to-originator ratio (%)	90% CI of ratio
$AUC_{0-t.obs}$ ng/mL*h	100.9	87.8 to 115.8
$AUC_{0-t.inf}$ ng/mL*h	98.9	83.0 to 123.4
C_{max} (ng/mL)	101.2	86.6 to 112.9

respectively, among those patients completing the protocol. In 3 cases (2 while on the originator and 1 on the generic) AEs forced the patient to leave the study.

4 | DISCUSSION

This is the first trial comparing originator and generic preparations of LDB in patients suffering from advanced PD. The study demonstrated the noninferiority of the *generic* LDB preparation compared to the *originator* by the evaluation of clinical efficacy and PK profiles. LD generic formulations may differ from the *originator* because of bioavailability or different PK characteristics which may result in unpredictable OFF periods and worsening of dyskinesia. This study showed that the generic and the originator formulation met the criteria for bioequivalence. The AUC, C_{max} and T_{max} for the originator and the generic were comparable after administration of a single dose of standard LDB. We found a large variability between subjects regarding PK characteristics of LD with both formulations, but this has already been described in literature.[21-25] This large variability has been attributed to a different gastric mobility and absorption rate across patients. Indeed, gastric emptying depends on several factors SUCH type of food ingested, LD intake and constipation, and may be a key factor in determining LD plasma concentration.[25,26] Moreover, gastric emptying time is delayed in patients with PD especially in those suffering from motor fluctuation.[24,25] Bioequivalence studies are usually performed on healthy volunteers assuming that efficacy and tolerability profiles verified in healthy subjects would apply to patients. Considering the frequency of gastrointestinal dysfunctions in PD patients and their impact on LD absorption, this assumption cannot be made in this disease since variability of blood concentrations with generic drugs may be unpredictable and result in a reduced therapeutic equivalence. Therefore, we decided to test the bioequivalence of the LDB generic formulation in a population of moderate–advanced PD patients, mimicking a real-life situation.

Patients may have preconceived negative expectations about the effectiveness of generic drugs, and this may reflect in a lessebo/nocebo effect during studies comparing originator and generic formulations. The UPDRS values and the CGI-I mean scores in this trial revealed comparable motor performance between the 2 treatments as assessed by both investigators and patients. Compared to placebo-controlled trials, the magnitude of change from baseline of the motor UPDRS (mUPDRS) tends to be larger in studies with active controlled comparators. In a meta-analysis published in 2014 by Mestre et al.,[27] the change from baseline of mUPDRS was reported to be 6.0 units in the placebo-controlled group *vs* 7.6 units in the active-controlled group. Therefore, the lessebo effect was estimated to be 1.60 mUPDRS units and tended to be higher for early PD patients and for studies with duration of <12 weeks. In our study, the difference in the mean changes reported at the end of each treatment period in mUPDRS was 1.05 units, below the value of 1.6 that defines lessebo effect and that Mestre et al.[27] considered clinically relevant. Subjects were also asked to express a drug preference between treatment A and B: 14 patients showed no preference, 14 expressed their preference towards the generic formulation and 9 towards the treatment with the originator. In our study, however, the majority of subjects expressed no preference between the 2 treatments or showed preference towards the generic formulation, showing that, if present, lessebo/nocebo effect due to negative expectations was clinically nonsignificant.

Noteworthy this study was performed with one brand of generic LDB and that generic preparations on the market may show a different bioavailability. PK equivalence between generic and originator formulation of LDB was also previously demonstrated in a single dose, randomized-sequence, open label crossover study performed in healthy volunteers.[28] However, attention needs to be paid to the possible variability among different brands of generics preparation. Moreover, switching from one generic to another may occur in clinical practice and doctors must be aware that this may be associated to even further plasma variability creating a potential risk of therapeutic *inequivalence*. To demonstrate clinical and PK equivalence, both generic and originator were over-encapsulated, which is the most widely used method of blinding in clinical trials. Even if it must be acknowledged that over-encapsulation may alter absorption, several studies have demonstrated that encapsulation does not significantly alter dissolution and bioequivalence of active compounds.[29,30] Furthermore, in this study were not used quarters of tablets in order to avoid excessive breaking or grinding of the active ingredient during the encapsulation process. Moreover, no backfill was used, eliminating

a possible interaction between the backfill and the gelatine capsules and the risk of dissolution problems of the active ingredient.

5 | CONCLUSIONS

Generic drugs represent an important opportunity for costs reduction for both patients and health care systems, resources that could alternatively be utilized to develop innovative drugs or to implement research. Unfortunately, generic preparations do not always satisfy patient's expectations, and this is particularly true in PD patients because of their sensitivity to minimal change in pharmacological activity. The present study demonstrated that the generic preparation of LDB tested in the study, is equivalent to the originator. The results are reliable because they were obtained in patients where not only the PK but also the pharmacodynamics were studied. Generic formulation can be used in PD patients, but they should be tested in patients and not only on normal volunteers.

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COMPETING INTERESTS

There are no competing interests to declare.

CONTRIBUTORS

M.T. wrote the manuscript and performed clinical evaluations, J.A. performed PK analysis and wrote PK methodology, C.I. performed statistical analysis on PK parameters and wrote PK results, D.B. revised the manuscript, M.C. performed blood collection and processing, C.F., P.G., L.V., FG.R. and M.O. performed clinical evaluations, S.B. performed clinical data analysis, wrote the statistical section and revised the manuscript, F.S. planned and directed the study and revised the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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