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Comparison of IPX066 with carbidopa–levodopa plus entacapone in advanced PD patients

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ABSTRACT

Background: IPX066, an investigational extended-release carbidopa–levodopa (CD-LD) preparation, has demonstrated a rapid attainment and prolonged maintenance of therapeutic LD plasma concentrations in advanced Parkinson's disease (PD). This phase-3 crossover study assessed its efficacy and safety vs. CD-LD plus entacapone (CL + E).

Methods: At baseline, all patients had motor fluctuations despite a stable regimen of CL + E or CD-LD-entacapone combination tablets (CLE). The study included a 6-week conversion from CL + E or CLE to IPX066, followed by two 2-week, double-blind crossover treatment periods in randomized order, one on IPX066 (and placebo CL + E), the other on CL + E (and placebo IPX066), separated by 1-week open-label IPX066 treatment. The primary efficacy measure was mean percent daily "off" time during waking hours (from patient diaries).

Results: Of 91 randomized patients, 84 completed the study. Their median daily LD dosage was 1495 mg from IPX066 and 600 mg from CL + E, corresponding, after correction for bioavailability, to an approximately 22% higher LD exposure on IPX066. Compared with CL + E, IPX066 demonstrated a lower percent "off" time (24.0% vs. 32.5%; $p < 0.0001$), lower "off" time (3.8 vs. 5.2 h/day; $p < 0.0001$), and higher "on" time without troublesome dyskinesia (11.4 vs. 10.0 h/day; $p < 0.0001$). Other endpoints, including patient-reported treatment preference, also favored IPX066 ($p < 0.05$). During double-blind treatment, 20.2% and 13.6% of patients reported adverse events on IPX066 and CL + E, respectively. The most common were dyskinesia (4 patients), insomnia (3), and confusional state (3) for IPX066, and fall (2) for CL + E.

Conclusions: In advanced PD, IPX066 showed improved efficacy, compared with CL + E, and appeared to be well tolerated.

1. Introduction

In Parkinson's disease (PD), no medical or surgical therapy has been shown to provide anti-parkinsonian benefits superior to those of levodopa (LD) [1]. However, as PD progresses, chronic LD treatment is associated with the development of motor complications, including motor fluctuations (such as wearing-off episodes, reflecting a loss of benefit between doses) and dyskinesia (which may occur at therapeutic LD plasma concentrations). Although motor fluctuations are considered to be late complications of PD, the ELLDOPA trial reported their emergence within 5–6 months after initiation of immediate-release (IR) carbidopa–levodopa (CD-LD) therapy [2,3]. In the extreme, patients may cycle between disabling dyskinesias during "on" time and disabling parkinsonism during "off" time.

Motor complications are thought to be caused by non-physiologic fluctuations in LD plasma concentrations [4], and are the primary reason for surgical interventions in PD [5]. Accordingly,

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many approaches have been employed to increase the duration of stable LD concentrations. Among them, entacapone acts as an inhibitor of catechol-O-methyl transferase (COMT), increasing LD bioavailability, extending the LD elimination half-life, and prolonging LD effects [6–8]. Co-administration of entacapone with CD-LD (CL + E) has been used to treat wearing-off [9–11]; however, frequent dosing is still required, especially in patients with advanced PD. For its part, the administration of entacapone in carbidopa–levodopa-entacapone (CLE) combination tablets [12] to patients with advanced PD has exhibited LD pharmacokinetics similar to those of sustained-release CD-LD formulations [13]. Hence, there is a continuing need for alternative CD-LD treatment options.

IPX066 (Impax Pharmaceuticals, a division of Impax Laboratories, Inc., Hayward, CA, USA) is an investigational extended-release (ER) formulation of CD-LD (1:4 ratio). In patients with advanced PD, it provided a rapid onset of clinical effects, which lasted for approximately 6 h after a single dose [14,15]. In the present study, it was compared with CL + E in advanced PD.

2. Methods

This phase 3, randomized, double-blind, double-dummy, crossover study evaluated IPX066 and CL + E in advanced PD patients who had been taking a stable dosage of CL + E or CLE. The study design (Fig. 1A) included a 6-week dose conversion from CL + E or CLE to IPX066, followed by two 2-week double-blind crossover treatment periods (in randomized order), one on IPX066, the other on CL + E, separated by a 1-week open-label IPX066 treatment period. The study was conducted in the US, Italy, Germany, and France, and was performed in accordance with the Declaration of Helsinki. All sites received Institutional Review Board (IRB) approval, and all patients provided written informed consent prior to participation (CinicalTrials.gov: NCT01130493).

2.1. Study population

Study participants had advanced idiopathic PD [16] at Hoehn-Yahr stage I–IV, diagnosed at age ≥30 years; ≥4 weeks of stable CL + E or CLE treatment with a dosing frequency ≥4 times/day and with a total LD IR dosage ≥400 mg/day; a 3-day mean "off" time ≥2.5 h/day (per PD diary); and a Mini-Mental State Examination score ≥26. Concomitant use of dopamine agonists, monoamine oxidase-B inhibitors, amantadine, or anticholinergics was permitted at stable dosage. Exclusion criteria included atypical or secondary parkinsonism; non-responsiveness to LD; prior neurosurgical PD treatment; active psychosis or current treatment with antipsychotics; a history of peptic ulcer disease, upper gastrointestinal hemorrhage, gastrointestinal surgery, narrow-angle glaucoma, malignant melanoma, or

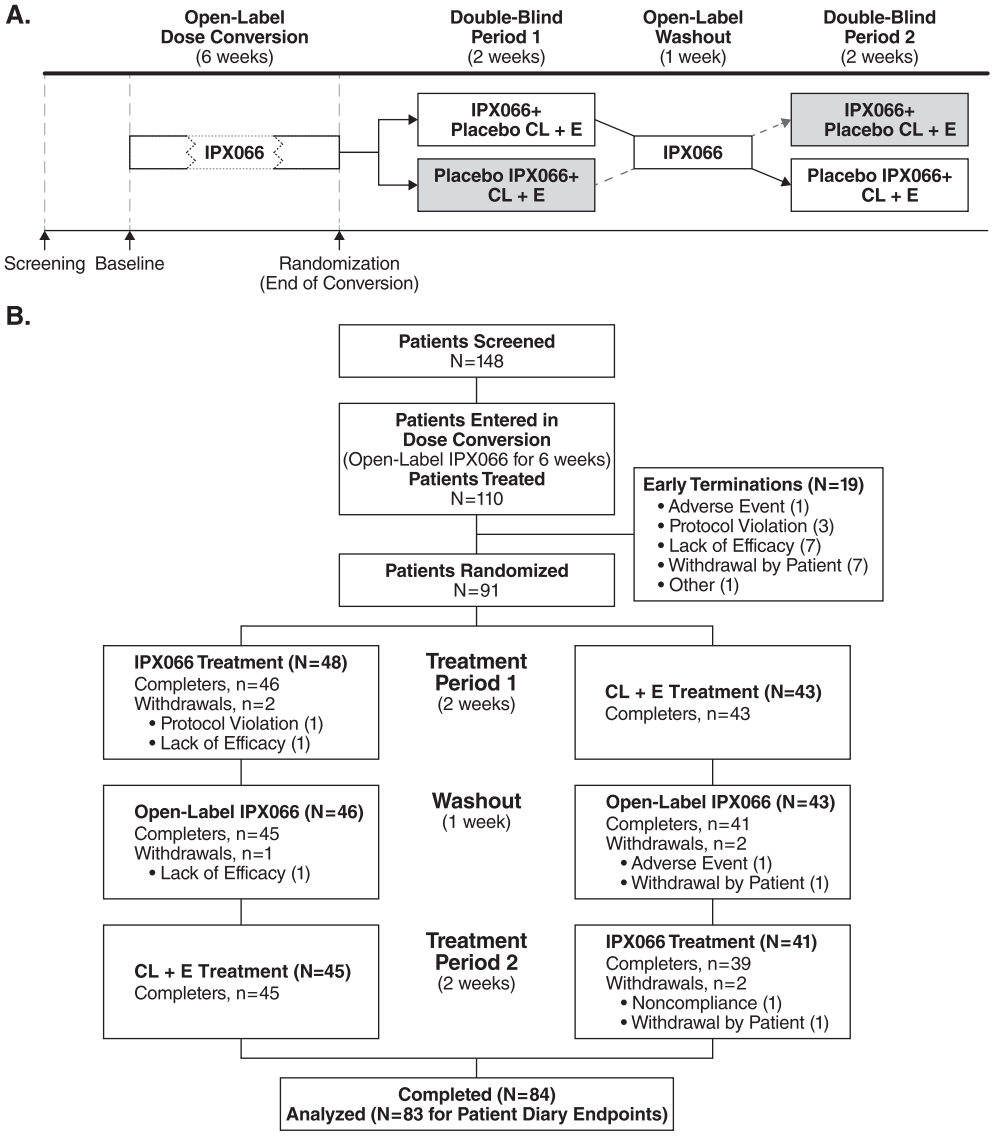

Fig. 1. Study design (A) and patient disposition (B).

myocardial infarction with residual arrhythmia; abnormal renal function; severe hepatic impairment; or prior participation in an IPX066 study.

2.2. Dosing

During 6-week dose conversion, each patient's initial dosage of open-label IPX066 was based on the patient's daily LD dosage at study entry, using a dose-conversion table provided in the study protocol. The initial dosing frequency was 3 times/day during waking hours. A bedtime dose was allowed if necessary. Dosing >5 times/day was not allowed. After dose conversion, using a two-period crossover design, patients were randomized to receive 2 weeks of double-blind IPX066 (and placebo CL + E) or double-blind CL + E (and placebo IPX066) in double-dummy fashion. IPX066 was administered as the individualized regimen achieved during dose conversion and CL + E as the patient's baseline regimen. Each patient then crossed to 2 weeks of the alternative double-blind treatment. Because the dosing frequency for IPX066 and CL + E likely were different for many patients, these patients took IPX066 (or placebo) and CLE (or placebo) at different times throughout the day. Between the two double-blind treatment periods, patients received 1 week of open-label IPX066. No dose adjustments were permitted post-randomization, and no CD-LD IR supplementation was allowed.

2.3. Study medications

IPX066 capsules (Impax Pharmaceuticals, a division of Impax Laboratories Inc., Hayward CA) were supplied in four CD/LD strengths: 23.75/95, 36.25/145, 48.75/195, and 61.25/245 mg. CL + E was administered as CD-LD IR (Sinemet® 25/100 mg; Merck & Co., Inc., Whitehouse Station NJ) plus entacapone (Comtan® 200 mg; Orion Pharma, Espoo, Finland). Matching placebos for IPX066, CD-LD IR, and entacapone were manufactured by Impax Laboratories. The placebo tablets for entacapone contained a quantity of riboflavin sufficient to mimic the potential urine discoloration due to entacapone.

2.4. Efficacy endpoints

The primary efficacy endpoint was mean percent "off" time during waking hours, based on patient diaries during the last 3 days of each double-blind treatment period. Key secondary efficacy measures included "off" time, "on" time without troublesome dyskinesia [17], Unified Parkinson's Disease Rating Scale (UPDRS) Part II + III scores (in the "on" state), and patient-reported preference for treatment. A responder analysis evaluated the proportion of study completers achieving improvement of at least 0.5, 1, 1.5, 2, and 3 h of reduction in "off" time from baseline.

Health-related quality-of-life outcomes were evaluated using the EuroQol 5D (EQ-5D) [18], the Medical Outcomes Study 36-item Short Form Survey (SF-36) [19], and the Parkinson's Disease Sleep Scale (PDSS) [20].

2.5. Safety

Safety was evaluated in all patients treated with at least one dose of any study medication, by parameters including reported adverse events (AEs), serious adverse events (SAEs), vital signs, and clinical laboratory and electrocardiographic assessments. AE incidence was assessed for each study period (i.e., dose conversion, each double-blind treatment, and washout), with each AE assigned to the period in which it started.

2.6. Statistical analyses

Sample-size determination is described in Supplementary Materials. Efficacy analyses included patients with at least 2 days of evaluable diary data from both double-blind treatment periods. For post-hoc sensitivity analyses, the worst available observations from patients who discontinued early were used for IPX066 treatment, and the best available observations for CL + E treatment; missing preferences for treatment were assigned to CL + E, and drop-outs were classified as non-responders to their uncompleted treatment.

All endpoints except patient preference for treatment and proportion of patients achieving thresholds of "off" time improvement were analyzed using a standard mixed-effect model with variance at a 0.05 significance level, treatment, sequence, and period as fixed effects, and inter- and intra-subject factors as random effects. Patient preference for treatment was analyzed by chi-square test. To control for type-1 error, key secondary endpoints were evaluated in a pre-specified hierarchical order ("off" time; "on" time without troublesome dyskinesia; UPDRS II + III score; patient preference for treatment) only if the primary measure showed significance between treatments. Measures analyzed without controlling for multiple comparisons included "on" time with troublesome dyskinesia, diary-based responder data, and scores on individual UPDRS parts, UPDRS Part II in the "off" state, EQ-5D, SF-36, and PDSS. Statistical analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary NC).

3. Results

Of 110 patients who entered the dose-conversion period, 91 were randomized, and 84 completed both crossover periods (Fig. 1B). Because one patient did not have diary data for the second double-blind period, 83 patients were analyzed for diary-related endpoints.

Baseline demographic and clinical characteristics of completers and of all randomized patients were similar (Table 1).

3.1. Dosing

Among the 84 completers, the median (mean ± SD) daily LD dosage during double-blind treatment was 1495 mg (1723 ± 713) for IPX066 and 600 mg (652 ± 252) for CL + E. For entacapone, the median (mean ± SD) daily dosage was 800 mg (943 ± 174). The median (mean ± SD) daily number of doses was 3.0 (3.5 ± 0.6) for IPX066, 5.0 (5.0 ± 1.2) for CD-LD IR, and 4.0 (4.7 ± 0.9) for entacapone.

3.2. Efficacy

On the primary endpoint (Fig. 2A), patients had a significantly lower mean percent "off" time during waking hours on IPX066 treatment than on CL + E treatment, at 24.0% ± 16.2% vs. 32.5% ± 21.9% ($p < 0.0001$), corresponding to a decrease from baseline of 34% vs. 10%. At baseline, patients had an average of 36.1% "off" time during waking hours; at the end of dose conversion, the average was 22.8%, a percentage similar to that observed during IPX066 treatment under blinded conditions. No treatment-period effect was observed ($p = 0.6997$).

Table 1
Demographic and clinical characteristics of the study population at baseline.

Variable	All randomized patients ($N = 91$)	Completer patients ($n = 84$)
Gender, *n* (%)		
Male	68 (74.7)	64 (76.2)
Female	23 (25.3)	20 (23.8)
Age, years, mean ± SD	64.1 ± 9.3	64.0 ± 9.1
Race, *n* (%)		
White	89 (97.8)	83 (98.8)
Other	2 (2.2)	1 (1.2)
Duration of PD, years, mean ± SD	10.0 ± 5.3	10.0 ± 5.4
Duration of levodopa treatment, years, mean ± SD	6.8 (5.0)	7.0 (5.0)
Duration of entacapone treatment, years, mean ± SD	2.8 (2.4)	2.9 (2.4)
Hoehn and Yahr score, mean ± SD	2.4 ± 0.7	2.4 ± 0.7
Total UPDRS score in "on" state, mean ± SD	41.4 ± 16.9	41.8 ± 17.1
Daily frequency of CD-LD IR, mean ± SD	5.0 ± 1.2	5.0 ± 1.2
Daily dose of CD-LD IR, mg, mean ± SD	660.4 ± 246.8	652.4 ± 251.9
Daily frequency of entacapone, mean ± SD	4.7 ± 0.8	4.7 ± 0.9
Daily dose of entacapone, mg, mean ± SD	940.7 ± 170.0	942.9 ± 174.4
"Off" time, % of waking day, mean ± SD	36.3 ± 16.1	36.1 ± 16.3[a]
"Off" time, hours/day, mean ± SD	5.9 ± 2.6	5.9 ± 2.7[a]
"On" time without troublesome dyskinesia, hours/day, mean ± SD	9.9 ± 2.9	9.8 ± 3.0[a]
"On" time without dyskinesia, hours/day, mean ± SD	7.8 ± 3.6	7.8 ± 3.6[a]
"On" time with non-troublesome dyskinesia, hours/day, mean ± SD	2.1 ± 2.8	2.1 ± 2.7[a]
"On" time with troublesome dyskinesia, hours/day, mean ± SD	0.6 ± 1.1	0.6 ± 1.2[a]

CD-LD IR, immediate-release carbidopa–levodopa; SD, standard deviation; PD, Parkinson's disease.
[a] $n = 83$.

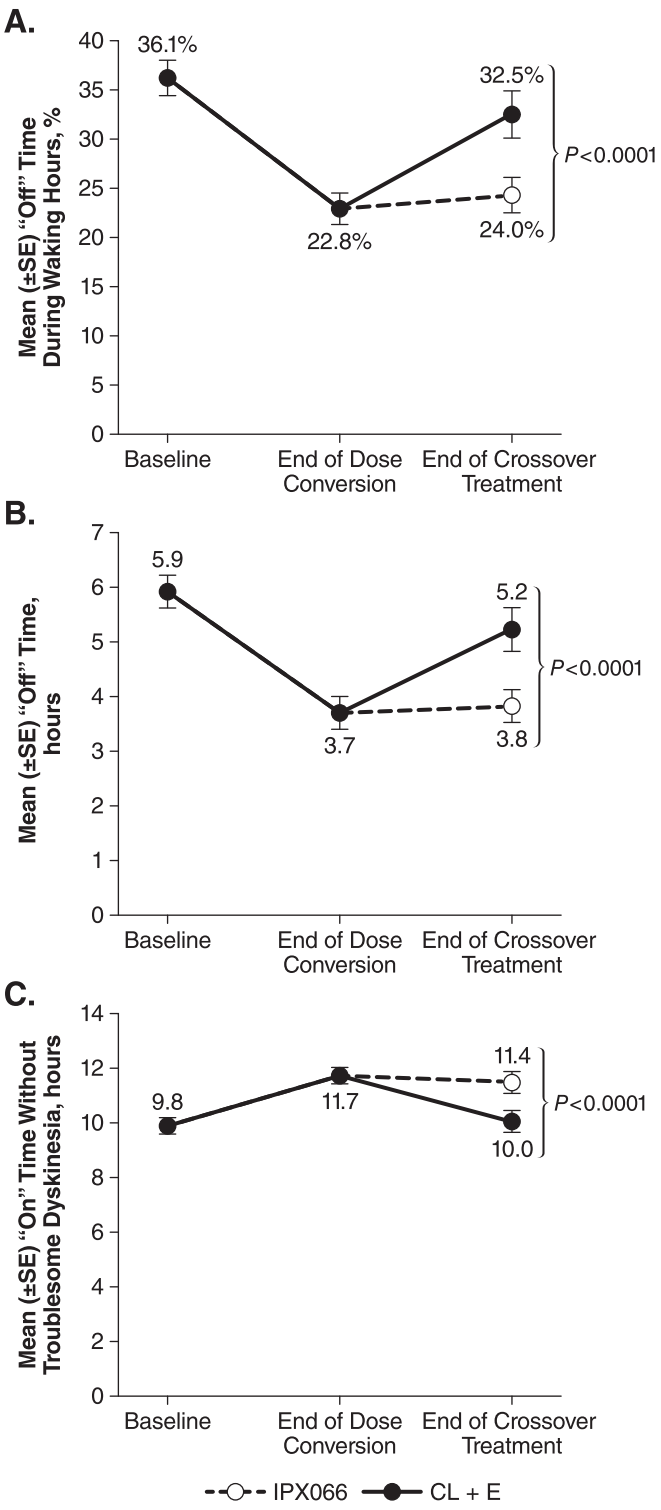

Fig. 2. Primary and key secondary efficacy endpoints among patients who completed the study and had complete PD Diary data ($n = 83$). A) Primary endpoint of mean percent "off" time during waking hours. B) Mean "off" time during waking hours per day. C) Mean "on" time without troublesome dyskinesia during waking hours per day.

Key secondary endpoints also significantly favored IPX066 (Fig. 2B and C). At end of study, the mean "off" time had decreased to 3.8 h/day during IPX066 and to 5.2 h/day during CL + E treatment, from 5.9 h/day at baseline, and the mean "on" time without troublesome dyskinesia had increased to 11.4 h/day during IPX066 and to 10.0 h/day during CL + E treatment, from 9.8 h/day at baseline. Hence, compared with CL + E treatment, IPX066 resulted in 1.4 h less daily "off" time and 1.4 h more daily "on" time without troublesome dyskinesia (both $p < 0.0001$). At endpoint, the treatments exhibited no significant difference in mean daily "on" time with non-troublesome dyskinesia (2.7 ± 3.3 h for IPX066 vs. 2.3 ± 3.3 h for CL + E; $p = 0.187$) or "on" time with troublesome dyskinesia (0.9 ± 1.9 h vs. 0.7 ± 1.6 h; $p = 0.3051$). At study end, UPDRS II + III scores in the "on" state averaged 29.3 ± 15.0 for IPX066 and 31.7 ± 14.9 for CL + E ($p = 0.0233$). Differences in treatment preference were statistically significant ($p = 0.0008$), with a higher proportion of completers preferring IPX066 (52.4%) relative to CL + E (27.4%) or no preference (20.2%).

In the study's post-hoc sensitivity analyses, which conservatively imputed data for 7 discontinued patients, mean percent "off" time during waking hours remained significantly lower for IPX066 than for CL + E (25.2% vs. 32.2%; $p = 0.0003$). Similarly, results significantly favored IPX066 on the four key secondary endpoints of mean "off" time ($p = 0.0005$), "on" time without troublesome dyskinesia ($p = 0.0002$), UPDRS II + III score ($p = 0.0437$), and treatment preference ($p = 0.0025$).

In responder analyses, the proportion of completers achieving each threshold of "off" time reduction was significantly higher for IPX066 than for CL + E (Supplementary Fig. 1). When all randomized patients were included (with drop-outs classified as non-responders), the proportions of patient achieving each threshold remained numerically higher for IPX066 (data not shown), with statistical significance for thresholds of 1, 1.5, and 3 h.

Among EQ-5D domains, only Anxiety/Depression showed a significantly higher proportion of patients reporting no problems during IPX066 than during CL + E treatment (61.9% vs. 52.4%; $p = 0.0443$). For the other domains and the visual-analog-scale assessment of current health status, results were directionally better for IPX066 but did not reach statistical significance. The SF-36 Physical Component Summary score significantly favored IPX066 over CL + E (40.8 ± 10.2 vs. 39.5 ± 9.9; $p = 0.0296$), but Mental Component Summary scores were similar (46.1 ± 10.7 vs. 45.6 ± 9.2; $p = 0.5330$). Total PDSS scores were also similar (103.5 ± 25.1 vs. 104.1 ± 24.5; $p = 0.7920$).

3.3. Safety

During IPX066 dose conversion, 30.9% of patients reported AEs (Table 2), with nausea (7.3%), vomiting (2.7%), fall (2.7%), and upper respiratory tract infections (2.7%) the most common AE types. During double-blind treatment, 20.2% of patients reported AEs on IPX066 and 13.6% did so on CL + E. The types reported by ≥ 2

Table 2
Adverse events ≥2% in any treatment.

AE preferred term	Dose conversion	Randomized crossover treatment		Open-label washout
	IPX066 ($n = 110$)	IPX066 ($n = 89$)	CL + E ($n = 88$)	IPX066 ($n = 89$)
Any AE, *n* (%)	34 (30.9)	18 (20.2)	12 (13.6)	12 (13.5)
Serious AEs, *n* (%)	2 (1.8)	1 (1.1)	0	1 (1.1)
AE leading to withdrawal	1 (0.9)	0	0	1 (1.1)
Common AEs, *n* (%)				
Nausea	8 (7.3)	1 (1.1)	0	0
Fall	3 (2.7)	1 (1.1)	2 (2.3)	0
Upper respiratory tract infection	3 (2.7)	0	0	0
Vomiting	3 (2.7)	1 (1.1)	0	0
Dyskinesia	1 (0.9)	4 (4.5)	0	1 (1.1)
Insomnia	1 (0.9)	3 (3.4)	0	0
Confusional state	0	3 (3.4)	0	0

AE, adverse event; CL + E, CD-LD plus entacapone.

patients were dyskinesia ($n = 4$; 4.5%), insomnia ($n = 3$; 3.4%), and confusional state ($n = 3$; 3.4%) on IPX066, and fall ($n = 2$; 2.3%) on CL + E. During open-label IPX066 washout, 13.5% of patients reported AEs. No AE type occurred in more than one patient.

Four patients reported SAEs, two during IPX066 dose conversion (hypercalcemia in one patient; atrial fibrillation, constipation, and chemical gastroenteritis in the other), one during double-blind IPX066 treatment (sciatica), and one during IPX066 washout (dehydration). None of the SAEs was considered treatment-related.

Two patients discontinued due to AEs, one during IPX066 dose conversion (dyspepsia, nausea, and vomiting) and one during open-label IPX066 treatment between the double-blind treatment periods (dyskinesia). No deaths occurred.

4. Discussion

At an approximately 22% higher LD exposure, but also a reduced dosing frequency, IPX066 significantly decreased percent "off" time during waking hours, by 34% during IPX066 treatment compared with 10% during CL + E treatment. A correspondingly greater decrease in "off" time (1.4 h) and a greater increase in "on" time without troublesome dyskinesia (1.4 h) were also observed. The effects of IPX066 on these measures during the double-blind period were similar to those observed after patients completed the open-label dose-conversion period. The effects are robust, as demonstrated by a post-hoc sensitivity analysis employing conservative imputation methods. The effects are also consistent with the 1.2 h greater reduction in "off" time observed in a 13-week randomized, double-blind comparison of IPX066 and CD-LD IR in advanced, fluctuating PD [21].

The plasma profile of IPX066 in patients with advanced PD exhibits a rapid onset and prolonged duration of LD absorption, as well as reduced LD peak/trough fluctuation [14,22]. Because this profile differs from those of other LD products, the present study included a 6-week dose-conversion period to allow time for dose adjustment. For the initial conversion from CLE or CL + E to IPX066, the dose-conversion table provided in the study protocol was based on the patient's total daily LD dosage in CLE or CL + E at study entry. As entacapone is known to increase LD bioavailability by approximately 35%–40% [23], the initial IPX066 doses provided by the table were approximately 30% higher than had been provided for converting CD-LD IR to IPX066 [21].

Among study completers, the daily LD dosage in patients' IPX066 was approximately 2.6 times the LD dosage in their CL + E regimens. With adjustment for a 47% bioavailability compared with the LD in CL + E (from a subset of study patients [24]), it can be estimated that the LD exposure provided by IPX066 was approximately 22% higher than that provided by CL + E. Nevertheless, "on" time with troublesome dyskinesia showed no significant difference between the two treatments.

Overall, IPX066 demonstrated acceptable tolerability. Although the incidence of AEs during double-blind treatment was higher on IPX066 (20.2%) than on CL + E (13.6%), the AEs were consistent with those reported in comparable studies of CD-LD or CL + E therapies [8,9,25,26], and were mainly neuropsychiatric or gastrointestinal. None of the SAEs was considered treatment-related.

A potential limitation of the present study is that it did not permit adjustment of CL + E regimens but allowed 6 weeks of dose conversion from CL + E to IPX066. Given the amount of "off" time at baseline, it is possible that increased LD exposure was necessary. If adjustment of the CL + E regimen had been permitted, the differences in treatment outcomes might have been smaller than were observed [27]. However, it can also be hypothesized that the patients might have undergone only minimal CL + E adjustment given that all were on a stable regimen of CLE or CL + E for ≥4 weeks at study entry. In a recent study comparing IPX066 to CD-LD IR in advanced PD patients who had been on a stable dose of CD-LD IR [21], a 3-week dose adjustment period for CD-LD IR resulted in an average increase of 31.1 mg/day of levodopa. Only 30.8% of patients increased their total daily dose, 60.4% had no change, and 8.8% decreased their daily dose of levodopa. The dose adjustment period resulted in a 0.42 h mean improvement in "off" time. If similar changes were seen with CL + E doses in the current study, it is unlikely that these changes would have resulted in a treatment effect matching that produced by IPX066. Additionally, entacapone is usually used to treat patients whose PD is inadequately controlled by CD-LD IR alone, and these patients had already been treated with CLE or CL + E for a mean 2.9 ± 2.4 years at enrollment.

Another potential limitation is that the double-blind treatment periods were only 2 weeks per treatment, which may be considered too short to identify true treatment differences. However, in the study comparing IPX066 and CD-LD IR in advanced PD referenced above [21], the motor effects observed 3 weeks after randomization were maintained for both treatments throughout the trial's 13-week double-blind treatment period. This is consistent with the general observation that in advanced PD, LD effects are mostly acute [28]. For these reasons, the design of the present study may be considered adequate to provide guidance on differences in efficacy and safety between IPX066 and CL + E in this patient population.

Despite these limitations, the consistency of the study's results across endpoints suggests that IPX066 treatment may improve the motor effects of LD and provide acceptable tolerability in PD patients inadequately treated with CLE or CL + E. The observed differences between the study's double-blind treatments appear to have been clinically meaningful to such patients, as a significantly greater proportion of patients preferred IPX066 to CL + E. The plasma profile of IPX066 may have contributed to the treatment's efficacy and safety. Larger and longer-term studies may be warranted to confirm the utility of IPX066 in advanced PD.

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Authors' roles

Fabrizio Stocchi contributed to study conception and design, acquisition of data, and analysis and interpretation of data, drafted and edited the manuscript, and approved the final version for publication. **Ann Hsu** contributed to study design, dosing guidance, endpoint selection, data analysis and interpretation, study report, manuscript writing and editing, and literature research. **Sarita Khanna** contributed to study design, endpoint selection, study conduct, data analysis and interpretation, safety data collection and analysis, and manuscript writing and editing. **Aaron Ellenbogen**,

Andreas Mahler, **Grace Liang**, and **Ulrich Dillmann** assisted with acquisition of data, analysis and interpretation of data, and revision of manuscript. **Robert Rubens** contributed to study design, endpoint selection, study conduct, data analysis and interpretation, manuscript editing, and safety data collection and analysis. **Sherron Kell** contributed to study design, endpoint selection, study conduct, data analysis and interpretation, study report, manuscript writing and editing, and safety data collection and analysis. **Suneel Gupta** contributed to study design, conduct, and data analysis.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.parkreldis.2014.08.004.

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