Effect of Concomitant Medications on the Safety and Efficacy of Extended-Release Carbidopa-Levodopa (IPX066) in Patients With Advanced Parkinson Disease: A Post Hoc Analysis

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Objectives: Extended-release (ER) carbidopa-levodopa (CD-LD) (IPX066) produces improvements in “off” time, on time without troublesome dyskinesia, and Unified Parkinson Disease Rating Scale scores compared with immediate-release (IR) CD-LD alone or CD-LD plus entacapone (CLE). Post hoc analyses of 2 ER CD-LD phase 3 trials evaluated whether the efficacy and safety of ER CD-LD relative to the respective active comparators were altered by concomitant medications (dopaminergic agonists, monoamine oxidase B [MAO-B] inhibitors, or amantadine).

Methods: ADVANCE-PD (n = 393) assessed safety and efficacy of ER CD-LD versus IR CD-LD plus CLE. ASCEND-PD (n = 91) evaluated ER CD-LD versus CLE. In both studies, IR- and CLE-experienced patients underwent a 6-week, open-label dose-conversion period to ER CD-LD prior to randomization. For analysis, the randomized population was divided into 3 subgroups: dopaminergic agonists, rasagiline or selegiline, and amantadine. For each subgroup, changes from baseline in PD diary measures (“off” time and “on” time with and without troublesome dyskinesia), Unified Parkinson Disease Rating Scale Parts II + III scores, and adverse events were analyzed, comparing ER CD-LD with the active comparator.

Results and Conclusions: Concomitant dopaminergic agonist or MAO-B inhibitor use did not diminish the efficacy (improvement in “off” time and “on” time without troublesome dyskinesia) of ER CD-LD compared with IR CD-LD or CLE, whereas the improvement with concomitant amantadine failed to reach significance. Safety and tolerability were similar among the subgroups, and ER CD-LD did not increase troublesome dyskinesia. For patients on oral LD regimens and taking a dopaminergic agonist, and/or a MAO-B inhibitor, changing from an IR to an ER CD-LD formulation provides approximately an additional hour of “good” on time.

Key Words: amantadine, dopaminergic agonist, extended release, levodopa, monoamine oxidase inhibitor

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Oral levodopa (LD) administered in combination with a peripherally active decarboxylase inhibitor such as carbidopa (CD) is the most widely used therapy for the symptomatic treatment of Parkinson disease (PD). However, prolonged use of LD and/or progression of the disease is often associated with the development of motor fluctuations, including end-of-dose “wearing off” and dyskinesia. Mechanisms leading to the development of the various patterns of motor fluctuations are incompletely understood, although there is evidence suggesting that pulsatile stimulation of dopamine receptors in the basal ganglia is involved. Several pharmacological strategies have been used to achieve more sustained plasma LD concentrations to manage, and possibly avoid, motor fluctuations associated with oral LD. These include the use of extended-release (ER) LD formulations and inhibitors of catechol-O-methyltransferase (COMT) and monoamine oxidase B (MAO-B).

In advanced PD, available adjunctive therapies can reduce “off” time associated with LD therapy, which in some studies exceeds 6 hours per day. In placebo-controlled studies, dopaminergic agonists and inhibitors of MAO-B have been shown to produce clinically meaningful reductions in “off” time as measured by patient home diaries and improved scores in the activities of daily living (Part II) and motor examination scores (Part III) of the Unified Parkinson Disease Rating Scale (UPDRS). Amantadine, a nonspecific glutamate N-methyl-D-aspartate receptor antagonist, reduces the severity and duration of LD-induced dyskinesia. A Cochrane Collaboration meta-analysis of efficacy and safety studies investigated adjunct oral treatments for PD patients with motor complications who were on stable immediate-release (IR) oral LD regimens and found that dopaminergic agonists were more effective at controlling parkinsonian symptoms than catechol-O-methyltransferase inhibitors or...
MAO-B inhibitors. The overall incidence of side effects was similar among the 3 groups. Current treatment guidelines reflect this conclusion. Extended-release CD-LD (IPX066, RYTARY, NUMIENT; Impax Laboratories, Inc, Hayward, Calif) is an oral CD-LD formulation that combines IR and ER components with the goal of more sustained plasma LD concentrations. Extended-release CD-LD pharmacokinetic studies have shown that LD plasma concentrations rise to a typical therapeutic range within 1 hour after oral dosing and are maintained for 4 to 6 hours. The safety and efficacy of ER CD-LD in patients with advanced PD have been evaluated in 2 multicenter, randomized, phase 3 trials (ADVANCE-PD and ASCEND-PD). In each of these trials, patients treated with ER CD-LD had less “off” time and more “on” time without troublesome dyskinesia and had improved UPDRS Part II + III scores compared with patients given IR CD-LD or IR CD-LD plus entacapone (CLE). Because a significant proportion of these advanced PD patients were receiving adjunctive PD therapies, we performed a post hoc analysis of data from these trials to evaluate if the efficacy and safety of ER CD-LD relative to the respective active comparators were affected by concomitant medications.

METHODS

Original Trial Designs

The study designs and protocols of the trials from which the current data were obtained have been published in detail. ADVANCE-PD and ASCEND-PD were phase 3, multinational, randomized, double-blind, double-dummy trials; ADVANCE-PD was a parallel-group study to assess the safety and efficacy of ER CD-LD versus IR CD-LD, whereas ASCEND-PD was a crossover study to evaluate ER CD-LD versus CLE. The primary clinical end point in both studies was “off” time as a percentage of waking hours. Both studies were performed in accordance with the Declaration of Helsinki. All sites received institutional review board approval, and each patient provided written informed consent prior to participation.

Safety was evaluated in all patients who received at least 1 dose of any study medication. Treatment-emergent adverse events (AEs) and serious AEs were recorded throughout the study.

Study Participants

Eligible patients had idiopathic PD (Hoehn and Yahr stage ≤4 in the “on” state), with motor fluctuations (≥2.5 hours of “off” time/d) despite taking equal to or greater than 400 mg LD/d in 4 doses or more per day, and a Mini-Mental State Examination score of 26 or greater. At enrollment, patients had at least 4 weeks of unchanged treatment with either an LD IR formulation or CLE at a dosing frequency of 4 or more times per day. Concomitant use of dopaminergic agonists, MAO-B inhibitors, amantadine, or anticholinergic drugs was permitted if doses were stable for at least 4 weeks prior to study entry. Key exclusion criteria included atypical or secondary parkinsonism, history of lack of response to LD, prior neurosurgical treatment for PD, severe dyskinesia, active psychosis (or treatment with antipsychotic medications), or prior participation in an ER CD-LD study.

Analysis

Efficacy

In each study, the randomized patient population was divided into 3 subgroups based on the use of concomitant medications at study entry: a dopaminergic agonist group, a MAO-B inhibitor group (rasagiline and selegiline), and an amantadine group. Patients could be receiving more than 1 of these adjunctive medications concurrently, and these patients were included in more than 1 subgroup for analysis. For each subgroup, the changes from baseline in PD diary measures (“off” time and “on” time with and without troublesome dyskinesia) and UPDRS sum of Parts II (activities of daily living) and III (motor examination) scores in the “on” state were analyzed, comparing ER CD-LD with the respective active comparator.

Safety Measures

Adverse event rates for the overall studies are reported in the primary articles for each study. Adverse events reported by 4% or more of patients during the double-blind portions of each study are reported for each treatment group within each concomitant medication subgroup.

Statistical Analyses

Post hoc analyses of the changes from baseline in PD diary measures and UPDRS Parts II and III scores at end of study were performed using a 2-way analysis of variance with subgroup variables of concomitant medication (with or without) and study treatment (ER CD-LD vs IR CD-LD or ER CD-LD vs CLE). Because of the exploratory nature of these analyses, no corrections or adjustments were made for multiple comparisons.

RESULTS

Patient Demographics

Patient demographics are summarized in Table 1. Totals of 393 and 91 patients were randomized in ADVANCE-PD and ASCEND-PD, respectively. Age, duration of PD, and duration of LD treatment were similar between or within studies according to concomitant medication use (Table 1). Of the patients randomized, at least 50% in both studies received a concomitant dopaminergic agonist. Fewer than 25% of patients took amantadine in either trial. Fewer than 25% of patients took selegiline or rasagiline in ADVANCE-PD, whereas 35% of patients took either one of these in ASCEND-PD.

Overall, there were more terminations in the ER CD-LD group (7.5% overall) when compared with those taking IR CD-LD (5.2% overall) and when taking a concomitant medication of the same class. Most of this difference could be accounted for by greater numbers of subjects voluntarily withdrawing from the study rather than by other factors. The number withdrawing because of AEs was similar between subgroups in ADVANCE-PD. In 9 patients each for both ER CD-LD and IR CD-LD (1.5% overall for ER CD-LD vs 1.6% for IR CD-LD), the numbers of discontinuations were similar between subgroups when there was no concomitant medication. There were only 4 early discontinuations in the ASCEND-PD study overall (all in the ER CD-LD subgroup), so no pattern could be discerned.

Levodopa doses given at baseline and after dose conversion were, in general, similar among subgroups. The mean daily dose (mg LD/d) conversion ratio of ER CD-LD to IR CD-LD was 2.0 to 2.1, depending on the concomitant medication subgroup, and for ER CD-LD to CLE, it was 2.5 to 2.9. The dosing frequencies were 3.6 and 3.5 doses/d for the ER CD-LD formulation compared with the 5 doses/d for the IR CD-LD and CLE formulations, respectively (Table 1).
Baseline PD Diary Measures

Parkinson disease diary measures at baseline are summarized in Table 2. In both studies, the ranges at baseline of mean daily “off” time, “on” time without troublesome dyskinesia, and “on” time with troublesome dyskinesia were 5.6 to 6.4 h/d, 9.7 to 10.3 h/d, and 0.2 to 0.8 h/d, respectively. There were no differences between baseline values for patients randomized to ER CD-LD versus IR CD-LD or ER CD-LD versus CLE with or without any of the concomitant medication subgroups.

Baseline PD Diary Measures

Table 2. Patient Demographics, and Baseline ER CD-LD Dosing Characteristics

| Patients randomized, n | Total | Dopaminergic Agonist | Amantadine | Selegiline/Rasagiline |
|------------------------|-------|----------------------|------------|-----------------------|
|                        | With  | Without              | With       | Without               |
| ADVANCE-PD             | 393   | 210                  | 183        | 84                    | 309                    | 96         | 297        |
| ASCEND-PD              | 91    | 58                   | 33         | 20                    | 71                     | 34         | 57         |
| Age, mean (SD), y      |       |                      |            |                       |                        |            |
| ADVANCE-PD             | 63.2 (9.4) | 62.5 (8.7)     | 64.1 (10.1)  | 61.6 (8.4)  | 63.7 (9.6)  | 61.7 (9.0)  | 63.7 (9.5)  |
| ASCEND-PD              | 64.1 (9.3) | 63.8 (9.1)     | 64.7 (9.9)  | 63.5 (7.0)  | 64.3 (9.9)  | 62.4 (9.3)  | 65.1 (9.3)  |
| Duration of PD, mean (SD), y |       |                      |            |                       |                        |            |
| ADVANCE-PD             | 7.4 (4.5)  | 8.0 (4.58)        | 6.8 (4.29)  | 7.9 (4.36)  | 7.3 (4.51)  | 7.8 (4.82)  | 7.3 (4.37)  |
| ASCEND-PD              | 10.0 (5.3) | 10.6 (4.98)      | 9.0 (5.67)  | 11.0 (5.37) | 9.8 (5.25)  | 8.9 (4.03)  | 10.7 (5.81) |
| Duration of treatment with LD, mean (SD), y |       |                      |            |                       |                        |            |
| ADVANCE-PD             | 5.8 (4.2)  | 8.0 (4.58)        | 6.8 (4.29)  | 6.5 (4.14)  | 5.6 (4.14)  | 7.8 (4.82)  | 7.3 (4.37)  |
| ASCEND-PD              | 6.8 (5.0)  | 6.7 (4.16)        | 7.0 (6.18)  | 6.3 (4.91)  | 6.9 (5.00)  | 6.3 (3.37)  | 7.1 (5.71)  |
| Baseline IR CD-LD dose, mean (SD), mg/d |       |                      |            |                       |                        |            |
| ADVANCE-PD             | 776 (353) | 749 (392)         | 790 (323)  | 766 (303)  | 767 (376)  | 709 (409)  | 787 (343)  |
| ASCEND-PD              | 660 (247) | 634 (213)         | 707 (294)  | 735 (332)  | 639 (215)  | 579 (210)  | 709 (256)  |
| Baseline IR CD-LD dose frequency, mean (SD), no. doses/d |       |                      |            |                       |                        |            |
| ADVANCE-PD             | 5.0 (1.6)  | 5.2 (1.9)         | 4.7 (1.2)  | 4.9 (1.5)  | 5.0 (1.9)  | 4.9 (1.5)  | 5.1 (1.8)  |
| ASCEND-PD              | 5.0 (1.2)  | 5.2 (1.3)         | 4.5 (0.9)  | 5.4 (1.6)  | 4.8 (1.0)  | 4.7 (1.0)  | 5.1 (1.3)  |
| Final ER CD-LD dose, mean (SD), mg/d |       |                      |            |                       |                        |            |
| ADVANCE-PD             | 1622 (744) | 1596 (810)        | 1651 (662) | 1582 (657) | 1632 (767) | 1424 (592) | 1686 (778) |
| ASCEND-PD              | 1792 (771) | 1695 (778)        | 1961 (740) | 1757 (884) | 1802 (743) | 1616 (767) | 1896 (760) |
| Final ER CD-LD dose frequency, mean (SD), no. doses/d |       |                      |            |                       |                        |            |
| ADVANCE-PD             | 3.6 (0.7)  | 3.5 (0.7)         | 3.6 (0.7)  | 3.6 (0.6)  | 3.6 (0.7)  | 3.6 (0.6)  | 3.6 (0.7)  |
| ASCEND-PD              | 3.5 (0.6)  | 3.5 (0.7)         | 3.4 (0.5)  | 3.6 (0.7)  | 3.5 (0.6)  | 3.4 (0.6)  | 3.5 (0.6)  |
| Dose conversion ratio, mean (SD) |       |                      |            |                       |                        |            |
| ADVANCE-PD (ER CD-LD/IR CD-LD) | 2.1 (0.6) | 2.1 (0.6)         | 2.0 (0.6)  | 2.1 (0.7)  | 2.0 (0.5)  | 2.0 (0.6)  | 2.1 (0.6)  |
| ASCEND-PD (ER CD-LD/CLE) | 2.8 (0.8) | 2.7 (0.8)         | 2.9 (0.6)  | 2.5 (0.8)  | 2.9 (0.7)  | 2.8 (0.7)  | 2.8 (0.8)  |

With/Without indicates with or without concomitant medication treatment.

Effects of Concomitant Dopaminergic Agonists

The decrease from baseline to end of double-blind treatment in “off” time was significantly greater in patients given ER CD-LD versus IR CD-LD (Fig. 1A) or ER CD-LD versus CLE (Fig. 1D) with or without concomitant dopaminergic agonist administration. The improvement in “on” time without troublesome dyskinesia was significantly greater with ER CD-LD versus IR CD-LD (Fig. 1B; ADVANCE-PD) and with ER CD-LD versus CLE (Fig. 1E; ASCEND-PD) in patients receiving a concomitant dopaminergic agonist. The increase in “on” time without troublesome dyskinesia with ER CD-LD in patients not taking a concomitant dopaminergic agonist was significantly greater only versus IR CD-LD (Fig. 1B). Relative to each study comparator, ER CD-LD did not significantly worsen “on” time with troublesome dyskinesia with or without a concomitant dopaminergic agonist (Figs. 1C, F).

Effect of Concomitant Selegiline or Rasagiline

Extended-release CD-LD produced significantly greater improvements in “off” time (Figs. 2A, D) and in “on” time without troublesome dyskinesia (Figs. 2B, E) versus IR CD-LD or CLE in patients with and without concomitant selegiline or rasagiline. There was no significant worsening of “on” time with troublesome dyskinesia with or without concomitant selegiline or rasagiline use in either study (Figs. 2C, F).

Effect of Concomitant Amantadine

Extended-release CD-LD caused significantly greater improvements in “off” time (Figs. 3A, D) and “on” time without troublesome dyskinesia (Figs. 3B, E) versus IR CD-LD or CLE only in patients not receiving concomitant amantadine treatment. There was no significant change in “on” time with troublesome dyskinesia with ER CD-LD, IR CD-LD, or CLE with or without concomitant amantadine (Figs. 3C, F).

Effect of Concomitant Medications on UPDRS Parts II and III Scores

Decreases (improvements) in UPDRS Parts II and III scores were significantly greater with ER CD-LD versus IR CD-LD and

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with ER CD-LD versus CLE in patients not taking a concomitant
dopaminergic agonist (Figs. 4A, D), selegiline or rasagiline
(Figs. 4B, E), or amantadine (Figs. 4C, F). Significantly greater
improvements in UPDRS Parts II and III scores were observed
with ER CD-LD versus IR CD-LD in those patients taking a
dopaminergic agonist (Fig. 4A), but not in patients taking the
other concomitant medications. Relative to CLE treatment, ER
CD-LD significantly improved UPDRS Parts II and III scores
only in those without concomitant medication.

Safety

Summaries of safety data are shown in Table 3 (ADVANCE-PD)
and Table 4 (ASCEND-PD).

The overall percentage of AEs for those patients taking
concomitant medications was similar for ER LD-CD and IR
CD-LD groups in ADVANCE-PD and for ER LD-CD and CLE
in ASCEND-PD.

For those taking concomitant medications, there were higher
incidences of dyskinesia and falls in the ER CD-LD group versus
the IR CD-LD group, even though the overall numbers were low.
The dyskinesia rate was higher for the ER CD-LD group versus
the CLE group only for those patients taking dopaminergic ago-
nists or selegiline or rasagiline. Adverse events of weight decrease
occurred in the ER CD-LD with concomitant medication groups,
and these were absent in the equivalent IR CD-LD groups.

Overall serious AEs have been reported in previous publica-
tions.24,25 In ADVANCE-PD, during the double-blind treatment
period, 11 patients (5%) in the ER CD-LD group reported 13
serious AEs. In the IR CD-LD group, there were 5 patients (3%)
who experienced 8 serious AEs. In ASCEND-PD, only 1 serious
AE (sciatica) occurred during double-blind treatment in an ER
CD-LD patient who was also taking a dopaminergic agonist and
a MAO inhibitor.26 The low number of serious AEs and absence
of any clear pattern did not allow for meaningful comparisons to
be made between subgroups. For any subgroup, only a single oc-
currence of each AE type was observed.

DISCUSSION

Relative to both comparator therapies, treatment with ER
CD-LD was associated with improvement in the key patient diary
measures (“off” and “on” time without troublesome dyskinesia),
regardless of whether the patient was taking a dopaminergic ago-
nist or a MAO-B inhibitor. Numerical improvements by ER
CD-LD versus each comparator were observed in patients treated
with concomitant amantadine, but these were not statistically
significant in either study. Relative to each comparator and
with all the concomitant medication subgroups, ER CD-LD
was not associated with worsening of troublesome dyskinesia.
Results of the UPDRS Parts II and III showed similar trends to
findings from the PD diary in favor of ER CD-LD. Extended-
release CD-LD treatment consistently improved scores compared
with IR CD-LD and CLE; however, the numerical improvement
was not statistically significant in patients receiving a MAO-B
inhibitor or amantadine.

The final dose ratio of preconversion and postconversion
to ER CD-LD from IR CD-LD were all 2.0 to 2.1, whereas from

### Table 2. Baseline PD Diary Measures and UPDRS Parts II and III Scores by Subgroup in ADVANCE-PD and ASCEND-PD

| Study          | Subgroup       | Double-blind Treatment | n   | Off Time, Mean (SD), h/d | Without Troublesome Dyskinesia | With Troublesome Dyskinesia | UPDRS Parts II and III Scores, Mean (SD) |
|----------------|----------------|------------------------|-----|-------------------------|--------------------------------|-----------------------------|------------------------------------------|
| ADVANCE-PD     | Dopaminergic agonist | With                   | IR CD-LD 100 | 5.9 (2.0)               | 10.3 (2.2)                      | 0.4 (1.1)                    | 31.0 (14.7)                             |
|                |                | ER CD-LD 110          | 6.2 (2.3)               | 10.2 (2.4)                      | 0.4 (1.0)                    | 30.8 (14.1)                             |
|                |                | Without IR CD-LD 92   | 5.9 (2.0)               | 9.9 (2.4)                       | 0.3 (0.9)                    | 34.0 (15.7)                             |
|                |                | ER CD-LD 91           | 5.9 (2.3)               | 9.7 (2.4)                       | 0.3 (0.9)                    | 34.1 (14.7)                             |
|                |                | With CLE 55           | 5.8 (2.8)               | 9.9 (3.2)                       | 0.7 (1.2)                    | 30.8 (15.1)                             |
|                |                | ER CD-LD 54           | 5.7 (2.8)               | 9.9 (3.2)                       | 0.8 (1.2)                    | 31.5 (15.4)                             |
|                |                | Without CLE 32        | 6.1 (2.5)               | 9.8 (2.5)                       | 0.3 (0.9)                    | 33.2 (15.4)                             |
|                |                | ER CD-LD 31           | 6.2 (2.5)               | 9.8 (2.5)                       | 0.4 (0.9)                    | 33.3 (15.7)                             |
| ADVANCE-PD     | Amantadine     | With                   | IR CD-LD 40            | 5.6 (1.9)                       | 10.3 (2.8)                      | 0.6 (1.3)                    | 35.2 (14.0)                             |
|                |                | ER CD-LD 44           | 6.0 (2.4)               | 10.0 (2.6)                      | 0.5 (1.1)                    | 35.2 (14.8)                             |
|                |                | Without IR CD-LD 152  | 6.0 (2.0)               | 10.1 (2.2)                      | 0.3 (0.9)                    | 31.7 (15.5)                             |
|                |                | ER CD-LD 157          | 6.1 (2.2)               | 10.0 (2.4)                      | 0.3 (0.9)                    | 31.5 (14.3)                             |
|                |                | With CLE 20           | 5.3 (2.1)               | 10.0 (2.7)                      | 0.8 (1.4)                    | 34.7 (18.7)                             |
|                |                | ER CD-LD 20           | 5.3 (2.1)               | 10.0 (2.7)                      | 0.8 (1.4)                    | 34.7 (18.7)                             |
|                |                | Without CLE 67        | 6.1 (2.8)               | 9.9 (3.0)                       | 0.5 (1.1)                    | 30.8 (14.0)                             |
|                |                | ER CD-LD 65           | 6.1 (2.8)               | 9.8 (3.0)                       | 0.5 (1.1)                    | 31.4 (14.4)                             |
| ADVANCE-PD     | Selegiline or rasagiline | With                   | IR CD-LD 48            | 6.2 (2.1)                       | 10.3 (2.1)                      | 0.2 (0.5)                    | 30.0 (13.2)                             |
|                |                | ER CD-LD 48           | 6.3 (2.6)               | 10.3 (2.1)                      | 0.4 (1.0)                    | 30.0 (14.1)                             |
|                |                | Without IR CD-LD 144  | 5.8 (1.9)               | 9.9 (2.5)                       | 0.4 (1.1)                    | 33.2 (15.8)                             |
|                |                | ER CD-LD 153          | 6.0 (2.7)               | 10.1 (2.4)                      | 0.4 (0.9)                    | 33.1 (14.5)                             |
| ADVANCE-PD     |                | With CLE 32           | 6.4 (2.5)               | 10.0 (2.8)                      | 0.4 (1.0)                    | 28.8 (15.0)                             |
|                |                | ER CD-LD 32           | 6.2 (2.5)               | 10.1 (2.8)                      | 0.4 (1.0)                    | 29.0 (15.1)                             |
|                |                | Without CLE 55        | 5.6 (2.7)               | 9.8 (3.0)                       | 0.7 (1.2)                    | 33.4 (15.1)                             |
|                |                | ER CD-LD 53           | 5.6 (2.7)               | 9.7 (3.0)                       | 0.7 (1.2)                    | 34.0 (15.4)                             |

With/Without indicates with or without concomitant medication treatment.
FIGURE 1. Effect of concomitant use of a dopaminergic agonist with ER CD-LD versus IR CD-LD (A–C) and ER CD-LD versus CLE (D–F) on PD diary measures. Changes from baseline to end of double-blind treatment were assessed for “off” time (A, D), “on” time without troublesome dyskinesia (B, E), and “on” time with troublesome dyskinesia (C, F). *P < 0.05 versus IR CD-LD within each subgroup. Error bars represent SEM.

FIGURE 2. Effect of concomitant use of selegeline or rasagiline with ER CD-LD versus IR CD-LD (A–C) and ER CD-LD versus CLE (D–F) on PD diary measures. Changes from baseline to end of double-blind treatment were assessed for “off” time (A, D), “on” time without troublesome dyskinesia (B, E), and “on” time with troublesome dyskinesia (C, F). *P < 0.05 versus IR CD-LD within each subgroup. Error bars represent SEM.
FIGURE 3. Effect of concomitant use of amantadine with ER CD-LD versus IR CD-LD (A–C) and ER CD-LD versus CLE (D–F) on PD diary measures. Changes from baseline to end of double-blind treatment were assessed for “off” time (A, D), “on” time without troublesome dyskinesia (B, E), and “on” time with troublesome dyskinesia (C, F). *P < 0.05 versus IR CD-LD within each subgroup. Error bars represent SEM.

FIGURE 4. Effect of concomitant use of medications with ER CD-LD versus IR CD-LD (A–C) and ER CD-LD versus CLE (D–F) on UPDRS Parts II and III scores in the “on” state. Changes from baseline to end of double-blind treatment were assessed with or without a concomitant dopaminergic agonist (A, D), selegiline or rasagiline (B, E), and amantadine (C, F). *P < 0.05 versus IR CD-LD within each subgroup. Error bars represent SEM. MAO, monoamine oxidase.
| AE                                    | % of Patients                                                                 |
|---------------------------------------|-------------------------------------------------------------------------------|
|                                       | With                | Without              | With                  | Without          | With                  | Without          | With                  | Without          | With                  | Without          |
|                                       | IR CD-LD (n = 100) | ER CD-LD (n = 110)  | IR CD-LD (n = 92)   | ER CD-LD (n = 91)   | IR CD-LD (n = 144) | ER CD-LD (n = 153) | IR CD-LD (n = 40)  | ER CD-LD (n = 44)  | IR CD-LD (n = 152) | ER CD-LD (n = 157) |
| Any AE                                | 40.0                | 43.6                 | 39.1                 | 42.9              | 41.7                | 47.9                | 38.9                 | 41.8              | 37.5                | 31.8              |
| Arthralgia                            | 0                   | 0.9                  | 3.3                  | 1.1              | 6.3                 | 0                   | 0.7                  | 1.3              | 0                   | 2.3              |
| Constipation                          | 2.0                 | 0.9                  | 0                   | 1.1              | 4.2                 | 0                   | 0                   | 1.3              | 5.0                 | 2.3              |
| Dizziness                             | 0                   | 0.9                  | 2.2                  | 4.4              | 2.1                 | 0                   | 0.7                  | 3.3              | 0                   | 2.3              |
| Dyskinesia                            | 2.0                 | 4.5                  | 0                   | 0               | 2.1                 | 4.2                 | 0.7                  | 2.0              | 0                   | 2.3              |
| Fall                                  | 3.0                 | 4.5                  | 1.1                  | 1.1              | 2.1                 | 6.3                 | 2.1                  | 2.0              | 2.5                 | 2.0              |
| Headache                              | 1.0                 | 0.9                  | 2.1                  | 1.1              | 0                   | 0                   | 2.1                  | 1.3              | 5.0                 | 2.3              |
| Muscle spasms                         | 2.0                 | 1.1                  | 1.1                  | 1.1              | 2.1                 | 4.2                 | 0.7                  | 0               | 0                   | 2.0              |
| Nausea                                | 0                   | 0.9                  | 2.2                  | 4.4              | 4.2                 | 0                   | 0.7                  | 3.9              | 2.5                 | 4.5              |
| Edema peripheral                      | 3.0                 | 2.7                  | 1.1                  | 0               | 4.2                 | 0                   | 1.4                  | 2.6              | 2.5                 | 0.0              |
| Upper respiratory tract infection     | 3.0                 | 1.8                  | 1.1                  | 2.2              | 2.1                 | 2.1                 | 2.1                  | 2.0              | 5.0                 | 2.3              |
| Urinary tract infection               | 2.0                 | 2.7                  | 2.2                  | 1.1              | 2.1                 | 6.3                 | 2.1                  | 0.7              | 0                   | 2.6              |
| Vomiting                              | 2.0                 | 0.9                  | 2.2                  | 1.1              | 2.1                 | 0                   | 2.1                  | 0.7              | 5.0                 | 2.3              |
| Weight decreased                      | 0                   | 3.6                  | 0                   | 0               | 0                   | 6.3                 | 0                   | 0.7              | 0                   | 4.5              |

With/Without indicates with or without concomitant medication treatment.
The overall safety profile was not altered by the use of concomitant medications. Dyskinesia is a well-documented adverse effect of all dopaminergic therapies. In the present study, there was an increased incidence of dyskinesia (reported as an AE) with ER CD-LD for those taking concomitant dopaminergic agonists and selegiline or rasagiline compared with prior regimens of IR CD-LD and CLE. However, the overall reporting rates for dyskinesia were low and did not translate into a significant increase in “on” time with troublesome dyskinesia (per patient diaries) for either of these concomitant therapies.

A limitation of the present analysis is that some of the patients may have received more than 1 class of concomitant therapy. Thus, the effects observed by one class may not be independent of the effects caused by the others and may be the result of interactions between the different classes. However, limiting patient selection to those given only 1 of the 3 classes used in the present analysis may have yielded sample sizes too low to allow for conclusions to be drawn.

In conclusion, the use of a concomitant dopaminergic agonist or MAO-B inhibitor did not diminish the efficacy of ER CD-LD compared with IR CD-LD or CLE, whereas the improvement observed with concomitant amantadine failed to reach statistical significance. Treatment with ER CD-LD also did not increase troublesome dyskinesia compared with IR CD-LD or CLE for any of the studied subgroups. Safety and tolerability were similar among the patient subgroups.

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