Preladenant as an Adjunctive Therapy With Levodopa in Parkinson Disease
Two Randomized Clinical Trials and Lessons Learned

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IMPORTANCE Preladenant is an adenosine 2A receptor antagonist that reduced “off” time in a placebo-controlled phase 2b trial in patients with Parkinson disease (PD). We sought to confirm its efficacy in phase 3 trials.

OBJECTIVE To evaluate preladenant as an adjunct to levodopa in patients with PD and motor fluctuations.

DESIGN, SETTING, AND PARTICIPANTS Two 12-week, phase 3, randomized, placebo-controlled, double-blind trials performed from July 15, 2010, to April 16, 2013. The setting included neurology clinics, clinical research centers, and hospitals in the Americas, the European Union, Eastern Europe, India, and South Africa. Participants included patients with moderate to severe PD taking levodopa who were experiencing motor fluctuations.

INTERVENTIONS In trial 1, a total of 778 eligible patients were randomized to the addition of preladenant (2 mg, 5 mg, or 10 mg twice daily), placebo, or rasagiline mesylate (1 mg/d) in a 1:1:1:1 ratio. In trial 2, a total of 476 eligible patients were randomized to the addition of preladenant (2 mg or 5 mg twice daily) or placebo in a 1:1 ratio.

MAIN OUTCOMES AND MEASURES The primary outcome measure was change in off time from baseline to week 12.

RESULTS In trial 1, neither preladenant nor rasagiline was superior to placebo in reducing off time from baseline to week 12. The differences vs placebo were −0.10 hour (95% CI, −0.69 to 0.46 hour) for preladenant 2 mg twice daily, −0.20 hour (95% CI, −0.75 to 0.41 hour) for preladenant 5 mg twice daily, −0.00 hour (95% CI, −0.62 to 0.53 hour) for preladenant 10 mg twice daily, and −0.30 hour (95% CI, −0.90 to 0.26 hour) for rasagiline mesylate 1 mg/d. In trial 2, preladenant was not superior to placebo in reducing off time from baseline to week 12. The differences vs placebo were −0.20 hour (95% CI, −0.72 to 0.35 hour) for preladenant 2 mg twice daily and −0.30 hour (95% CI, −0.86 to 0.21 hour) for preladenant 5 mg twice daily. Preladenant was well tolerated, with the most common adverse event that showed an increase over placebo in both trials being constipation (6%-8% for preladenant vs 1%-3% for placebo).

CONCLUSIONS AND RELEVANCE In these phase 3 trials, preladenant did not significantly reduce off time compared with placebo. That the active control rasagiline also failed to demonstrate a significant reduction in off time suggests that issues of study design or conduct may have affected these trials.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01155466 and NCT01227265
Randomized Clinical Trials of Preladenant With Levodopa in PD

The primary hypothesis in each trial was that at least 1 dosage of preladenant is superior to placebo as measured by change from baseline to week 12 in mean off time. The primary efficacy end point was analyzed using a constrained longitudinal data analysis approach with treatment, time, and treatment × time interaction as fixed effects and with patient as a random effect. The least-squares mean response and pairwise differences between preladenant dosages and placebo, along with 95% CIs, are reported. Using the same model, a comparison of rasagiline vs placebo was performed in trial 1. The efficacy population (full analysis set) consisted of all randomized patients with baseline data and postrandomization end point data after at least 1 dose of study medication.

Key secondary measures were the proportion of responders (≥30% reduction in mean off time from baseline to week 12) and change from baseline in mean on time without troublesome dyskinesia. Other secondary end points were analyzed but were uninformative and are not reported herein except for UPDRS part 3 scores.

Multiplicity was controlled through prespecified sequential testing procedures (eMethods in Supplement 3), whereby starting with the primary end point, the highest preladenant dosage was tested against placebo. If significant (P ≤ .05), the next pre-

Patients
Both trials enrolled patients with moderate to severe PD who were experiencing motor fluctuations. Key inclusion criteria included diagnosis of PD based on the UK Parkinson’s Disease Society Brain Bank criteria,18 with Hoehn-Yahr stage between 2.5 and 4, and receipt of a stable, optimal treatment regimen, including levodopa, and experience of motor fluctuations with a minimum of 2 hours per day off time (per 3-day PD diary19). Stable dosages of dopamine agonists, entacapone, amantadine hydrochloride, and anticholinergics were permitted. Monoamine oxidase type B inhibitors were prohibited. Key exclusion criteria included hallucinations, prior surgery for PD, impulse control disorders, drug-induced or atypical parkinsonism, cognitive impairment (Montreal Cognitive Assessment20 score <24 in trial 1 and <22 in trial 2), and untreated major depressive disorder (Diagnostic and Statistical Manual of Mental Disorders [Fourth Edition]21 criteria or a Beck Depression Inventory II22 score ≥19), as well as other significant conditions that could interfere with assessments or participation (eg, psychotic disorder, stroke, and head injury).

Primary Outcomes and Efficacy and Safety Assessments
The primary outcome measure was change in off time from baseline to week 12. Patients used a PD diary19 to denote their predominant status every half-hour over 24 hours to indicate whether they were off, on without dyskinesia, on with nontroublesome dyskinesia, or asleep. Patients underwent PD diary training and concordance testing during screening. They then completed 3-day sets of diaries at baseline and weeks 2, 4, 8, and 12. The Unified Parkinson’s Disease Rating Scale23 (UPDRS) parts 1 through 4 were administered at baseline, day 1, and weeks 2, 4, 8, and 12. Safety was assessed by review of adverse events, laboratory values, vital signs, and electrocardiograms.

Statistical Analysis
The primary hypothesis in each trial was that at least 1 dosage of preladenant is superior to placebo as measured by change from baseline to week 12 in mean off time. The primary efficacy end point was analyzed using a constrained longitudinal data analysis approach with treatment, time, and treatment × time interaction as fixed effects and with patient as a random effect. The least-squares mean response and pairwise differences between preladenant dosages and placebo, along with 95% CIs, are reported. Using the same model, a comparison of rasagiline vs placebo was performed in trial 1. The efficacy population (full analysis set) consisted of all randomized patients with baseline data and postrandomization end point data after at least 1 dose of study medication.

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Multiplicity was controlled through prespecified sequential testing procedures (eMethods in Supplement 3), whereby starting with the primary end point, the highest preladenant dosage was tested against placebo. If significant (P ≤ .05), the next pre-

Methods
Overview
We conducted two 12-week, phase 3, randomized, placebo-controlled, double-blind trials in patients with PD and motor fluctuations. These trials were identical in design except for treatment arms. In trial 1, patients were randomized to the addition of preladenant (2 mg, 5 mg, or 10 mg twice daily), placebo, or rasagiline mesylate active control (1 mg/d). In trial 2, patients were randomized to the addition of preladenant (2 mg or 5 mg twice daily) or placebo. The study protocols can be found in Supplement 1 and Supplement 2.

Trial 1 was conducted at 121 sites in Eastern Europe, the European Union, India, Latin America, North America, and Turkey from July 15, 2010, to December 20, 2012. Trial 2 was conducted at 88 sites in Eastern Europe, Latin America, North America, and South Africa from March 14, 2011, to April 16, 2013. The trials were conducted in accord with principles of good clinical practice and were approved by appropriate institutional review boards and regulatory agencies. Written informed consent was obtained from each patient before participation.

Patients were randomized to treatment (Figure 1) using a computer-generated allocation schedule prepared by Merck & Co, Inc and implemented through an interactive voice response system. Investigators, site staff, patients, and monitoring staff remained masked to treatment allocation throughout the trials.
specified test of preladenant vs placebo was evaluated. Formal hypothesis testing stopped once a nonsignificant difference was encountered. However, nominal $P$ values were still calculated.

**Power**

For each trial, the planned sample size was 150 patients per treatment group. This number provided at least 90% power to detect a difference between preladenant and placebo of 1 hour in change from baseline to week 12 in mean off time given an SD of 2.6 hours (as observed in the phase 2b study) and a 2-sided $\alpha = .05$.

**Post Hoc Investigations (Trial 1 Only)**

Once results of the studies were known, several post hoc investigations were undertaken. These post hoc analyses focused on trial 1 given that this trial included an active control arm (rasagiline) that failed to demonstrate efficacy. Investigations included an analysis of the integrity of the randomization process and treatment administration. In addition, a pharmacokinetic analysis evaluated whether expected plasma levels for randomized medications were achieved. The potential effect of caffeine consumption at baseline was evaluated by adding a caffeine term to the
primary analysis model. Additional analyses evaluated results according to geographic area and time when patients entered the trial.

Results

Patients
In trial 1, a total of 778 eligible patients were randomized to the addition of preladenant (2 mg, 5 mg, or 10 mg twice daily), placebo, or rasagiline mesylate (1 mg/d) in a 1:1:1:1 ratio. The full analysis set included 769 patients, and 106 discontinued treatment (Figure 1A). In trial 2, a total of 476 eligible patients were randomized to the addition of preladenant (2 mg or 5 mg twice daily) or placebo in a 1:1:1 ratio. The full analysis set included 473 patients, and 50 discontinued treatment (Figure 1B). In both studies, discontinuations were similar across treatment groups. Patient characteristics are summarized in Table 1. Baseline demographics were broadly similar between the 2 trials in terms of patient age and PD history. Treatment groups were similar in baseline disease severity.

Efficacy
In trial 1, neither preladenant nor rasagiline was superior to placebo in reducing off time from baseline to week 12 (eFigure 1A in Supplement 3). The differences vs placebo were −0.10 hour (95% CI, −0.69 to 0.46 hour) for preladenant 2 mg twice daily, −0.20 hour (95% CI, −0.75 to 0.41 hour) for preladenant 5 mg twice daily, and −0.10 hour (95% CI, −0.69 to 0.46 hour) for rasagiline 1 mg/d.

Table 1. Baseline Characteristics of Treated Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Trial 1</th>
<th>Trial 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>61.6 (9.3)</td>
<td>62.6 (8.5)</td>
</tr>
<tr>
<td>Male sex, No. (%)</td>
<td>97 (63.0)</td>
<td>78 (51.0)</td>
</tr>
<tr>
<td>PD duration, median (range), y</td>
<td>8.5 (1.2-25.2)</td>
<td>8.2 (2.0-23.6)</td>
</tr>
<tr>
<td>Levodopa dosage, mg/d</td>
<td>625 (125-3500)</td>
<td>681 (100-2000)</td>
</tr>
<tr>
<td>Hoehn-Yahr stage, No. (%)a</td>
<td>2.5 68 (44.2) 70 (45.8) 69 (45.1) 63 (40.6) 63 (40.9) 89 (56.7) 76 (48.4) 79 (49.7)</td>
<td>3 72 (46.8) 73 (47.7) 76 (49.7) 78 (50.3) 77 (50.0) 66 (42.0) 74 (47.1) 68 (42.7)</td>
</tr>
<tr>
<td>Region, No. (%)b</td>
<td>Eastern Europe 50 (32.1) 60 (38.7) 67 (42.9) 64 (41.3) 66 (42.3) 53 (33.5) 59 (37.1) 52 (32.7)</td>
<td>European Union 46 (29.5) 42 (27.1) 43 (27.6) 41 (26.5) 41 (26.3) 0 0 0</td>
</tr>
<tr>
<td>South Africa 0</td>
<td>0</td>
<td>0</td>
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</tbody>
</table>

Abbreviations: COMT, catechol-O-methyl transferase; PD, Parkinson disease.  
* The table does not include a small number of patients (maximum of 2 per treatment group) who had a Hoehn-Yahr stage of 2.  
b Based on randomized patients (see study flowcharts for sample sizes).  
** Includes levodopa combination treatments such as levodopa plus carbidopa.  
Primarily entacapone.  
Based on the full analysis set (see study flowcharts for sample sizes).
twice daily, −0.00 hour (95% CI, −0.62 to 0.53 hour) for preladenant 10 mg twice daily, and −0.30 hour (95% CI, −0.90 to 0.26 hour) for rasagiline mesylate 1 mg/d (Table 2). The percentage of responders with at least 30% decrease in off time at week 12 was similar among the preladenant, placebo, and rasagiline groups and ranged from 31.0% to 36.1%. Both the odds ratios and the proportions of responders showed no significant differences between preladenant or rasagiline vs placebo. All preladenant groups and the rasagiline group had numerically larger increases in on time without troublesome dyskinesia than the placebo group; however, none of the preladenant or rasagiline vs placebo differences were significant, nor was there a dose response. In general, changes in UPDRS part 3 scores were similar among treatments, with no significant differences from placebo other than for rasagiline at week 12 (eFigure 2A in Supplement 3).

In trial 2, preladenant was not superior to placebo in reducing off time from baseline to week 12 (eFigure 1B in Supplement 3). The differences vs placebo were −0.20 hour (95% CI, −0.72 to 0.35 hour) for preladenant 2 mg twice daily and −0.30 hour (95% CI, −0.86 to 0.21 hour) for preladenant 5 mg twice daily (Table 2). Mean increases in on time without troublesome dyskinesia at week 12 were similar (0.6, 0.7, and 0.5 hour) among treatment groups, and there were approximately 37% responders in the preladenant groups compared with 30.5% for the placebo group. Baseline UPDRS part 3 scores were similar across treatment groups and ranged from 26.2 to 27.7 points. In general, changes from baseline were similar among treatments, with no significant differences from placebo other than for preladenant 5 mg twice daily at week 12 (eFigure 2B in Supplement 3).

### Table 2. Key Efficacy Results at Week 12 (Full Analysis Set)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Preladenant, 2 mg Twice Daily</th>
<th>Preladenant, 5 mg Twice Daily</th>
<th>Preladenant, 10 mg Twice Daily</th>
<th>Placebo</th>
<th>Rasagiline Mesylate, 1 mg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trial 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean off time, h</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline</td>
<td>−0.9</td>
<td>−0.9</td>
<td>−0.8</td>
<td>−0.8</td>
<td>−1.1</td>
</tr>
<tr>
<td>Difference vs placebo (95% CI)</td>
<td>−0.10 (−0.69 to 0.46)</td>
<td>−0.20 (−0.75 to 0.41)</td>
<td>−0.00 (−0.62 to 0.53)</td>
<td>NA</td>
<td>−0.30 (−0.90 to 0.26)</td>
</tr>
<tr>
<td>P value</td>
<td>.70</td>
<td>.56</td>
<td>.87</td>
<td>NA</td>
<td>.28</td>
</tr>
<tr>
<td>Responders with ≥30% decrease in off time at 12 wk, %</td>
<td>31.0</td>
<td>33.3</td>
<td>33.8</td>
<td>33.9</td>
<td>36.1</td>
</tr>
<tr>
<td>Difference vs placebo (95% CI)</td>
<td>−3.60 (−14.97 to 7.84)</td>
<td>−0.70 (−12.36 to 10.93)</td>
<td>−0.50 (−12.00 to 10.95)</td>
<td>NA</td>
<td>1.90 (−9.81 to 13.58)</td>
</tr>
<tr>
<td>P value*</td>
<td>.61</td>
<td>.92</td>
<td>.98</td>
<td>NA</td>
<td>.71</td>
</tr>
<tr>
<td>Mean on time without troublesome dyskinesia, h</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Change from baseline</td>
<td>0.8</td>
<td>0.9</td>
<td>0.5</td>
<td>0.4</td>
<td>0.7</td>
</tr>
<tr>
<td>Difference vs placebo (95% CI)</td>
<td>0.40 (−0.21 to 1.09)</td>
<td>0.50 (−0.18 to 1.12)</td>
<td>0.20 (−0.49 to 0.80)</td>
<td>NA</td>
<td>0.40 (−0.29 to 1.01)</td>
</tr>
<tr>
<td>P value</td>
<td>.18</td>
<td>.16</td>
<td>.64</td>
<td>NA</td>
<td>.28</td>
</tr>
<tr>
<td><strong>Trial 2</strong></td>
<td></td>
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<tr>
<td>Mean off time, h</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline</td>
<td>−1.0</td>
<td>−1.1</td>
<td>NA</td>
<td>−0.8</td>
<td>NA</td>
</tr>
<tr>
<td>Difference vs placebo (95% CI)</td>
<td>−0.20 (−0.72 to 0.35)</td>
<td>−0.30 (−0.86 to 0.21)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>P value</td>
<td>.49</td>
<td>.24</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Responders with ≥30% decrease in off time at 12 wk, %</td>
<td>37.1</td>
<td>36.9</td>
<td>NA</td>
<td>30.5</td>
<td>NA</td>
</tr>
<tr>
<td>Difference vs placebo (95% CI)</td>
<td>7.00 (−4.17 to 18.05)</td>
<td>6.50 (−4.63 to 17.61)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>P value*</td>
<td>.24</td>
<td>.26</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Mean on time without troublesome dyskinesia, h</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline</td>
<td>0.6</td>
<td>0.7</td>
<td>NA</td>
<td>0.5</td>
<td>NA</td>
</tr>
<tr>
<td>Difference vs placebo (95% CI)</td>
<td>0.10 (−0.47 to 0.63)</td>
<td>0.10 (−0.44 to 0.67)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>P value</td>
<td>.78</td>
<td>.68</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not applicable. *P value is for the estimated odds ratio based on a generalized linear mixed model with baseline mean off time (hours per day) as a covariate, treatment × time interaction as a fixed effect, and patient as a random effect.
mon adverse event that showed an increase for preladenant over placebo was constipation (5.7% [26 of 460] vs 0.6% [1 of 155]). Few patients discontinued treatment because of adverse events, including 7.2% (33 of 460) receiving preladenant, 11.7% (18 of 154) receiving rasagiline, and 5.2% (8 of 155) receiving placebo. One death was reported, a respiratory arrest in the placebo group, considered by the investigator to be unlikely related to the study drug. The most common adverse event that showed an increase for preladenant over placebo was constipation (5.7% [26 of 460] vs 0.6% [1 of 155]). The most common adverse event that showed an increase for rasagiline over placebo was dyskinesia, occurring in 4.8% (22 of 460) receiving preladenant, 13.6% (21 of 154) receiving rasagiline, and 5.2% (8 of 155) receiving placebo.

In trial 2, preladenant was generally well tolerated, although the incidence of adverse events was higher for preladenant (occurring in 60.5% [190 of 314]) than placebo (occurring in 45.9% [73 of 159]). Few patients (5.1% [16 of 314]) of those receiving preladenant and 2.5% (4 of 159) of those receiving placebo discontinued treatment because of adverse events. One death was reported, a suicide (self-inflicted gunshot wound to the chest) in the preladenant 2 mg twice daily group, which was considered possibly related to the study drug by the investigator. The most common adverse event that showed an increase for preladenant over placebo was constipation (8.0% [25 of 314] vs 2.5% [4 of 159]).

**Post Hoc Analyses (Trial 1 Only)**

Investigations determined that the randomization code and treatments were correctly administered. Treatment groups in trial 1 were generally comparable in terms of demographics, baseline disease characteristics, and concomitant medications (including caffeine use). Review of demographic data and baseline disease characteristics did not reveal any notable differences between the phase 2b trial and the phase 3 trials or differences vs other similar published PD trials (eTable 2 in Supplement 3). Plasma concentrations of preladenant in trial 1 were largely consistent with those in the phase 2b trial (eTable 3 in Supplement 3). The observed mean steady-state rasagiline level in trial 1 was 2.4 ng/mL at 2 hours after dosing, similar to previous trials. Baseline caffeine use was not associated with off time change from baseline (P = .40 for <1 vs ≥1 cup per day and P = .54 for <1 vs >1 cup per day).

Analyses of potential regional differences (Table 3) found that Turkey, India, and Latin America had the largest mean reductions in off time in the placebo group (range, −1.00 hour to −2.15 hours), leading to numerically greater reductions in off time in the placebo group than in the preladenant or rasagiline groups. The mean placebo group reductions in off time were smaller in North America, the European Union, and Eastern Europe (range, −0.45 to −0.76 hour), leading to treatment responses that were directionally consistent with expectations that rasagiline and preladenant would show benefit vs placebo. However, improvements were still modest, with reductions from −0.39 hour to −1.18 hour in off time for preladenant 5 mg twice daily vs placebo and reductions from −0.57 hour to −0.71 hour in off time for rasagiline 1 mg/d vs placebo. There was no evidence of a dose response in the preladenant groups in any region.

Analyses by enrollment found that the first 50% of patients to be enrolled in trial 1 took approximately 18 months to enroll, whereas the second 50% took only approximately 9 months. Notably, patients in the placebo arm enrolled in the first half had a small response (reduction of −0.03 hour in off time) compared with patients enrolled in the second half (reduction of −1.40 hour in off time) (Figure 2). In addition, reductions in off time in the preladenant and rasagiline arms were slightly larger in the first half. Overall, patients randomized to preladenant (5 mg or 10 mg twice daily) or rasagiline enrolled in the first half demonstrated significant improvement vs placebo in reduction in off time (approximately 1 hour or more) (eTable 4 in Supplement 3).
Discussion

In these phase 3 trials, preladenant did not significantly reduce off time compared with placebo. However, because the active control (rasagiline) also failed to demonstrate a significant reduction in off time, it is not possible to determine from these results whether they represent a finding of inefficacy for preladenant or are related to issues of study design or conduct.

All 3 A2A antagonists (istradefylline, preladenant, and tozadenant) have yielded positive results in reducing off time in phase 2 trials (eTable 5 in Supplement 3).8-10,17 However, istradefylline had mixed phase 3 results,11-14 and our 2 preladenant trials failed (while tozadenant has not yet completed a phase 3 trial). We also note that the designs of the phase 3 trials have been essentially the same as those of the phase 2 trials, which suggests that A2A antagonists may have efficacy as adjuncts to levodopa but that problems with the execution of the phase 3 trials have hindered our ability to demonstrate this efficacy.

Demonstrating reduction in off time by diaries requires enrolling patients who actually have motor fluctuations, who can accurately recognize the various PD motor states (on, off, and dyskinesia), and who will accurately record those states over time in their diaries. Therefore, the investigator must select patients who actually have PD, confirm that the patient has true motor fluctuations, teach the patient to recognize the PD motor states, and verify that the patient understands them. It is then up to the patient to complete the diary in a timely and accurate manner. It seems likely that these requirements would be easiest to accomplish at a small number of expert sites with a successful clinical trial track record and a large population of well-known patients from which to draw, which appears to be the case for phase 2 trials but becomes more difficult in phase 3 trials, when more sites and more participants are required. In fact, the negative phase 3 studies enrolled the most patients (eTable 5 in Supplement 3).

In our post hoc analyses of trial 1, we identified a large placebo effect in Turkey, India, and Latin America, with numerically greater reductions in off time in these regions in the placebo group than in the preladenant or rasagiline groups. The exact reason for this finding is not known, but a large placebo response was also observed in a phase 3 monotherapy trial of preladenant in Latin America, India, Turkey, and Eastern Europe compared with North America and the European Union.27 We are also aware of a phase 2 trial of fipamezole as an antidyskinetic agent in which benefit was demonstrated in the United States but not in India.28 The differences could potentially be owing to clinical trial experience, cultural or language variations, genetic variation, or as yet unidentified reasons. Because no stratification or block randomization was used, our subgroup analyses may be subject to bias because they do not represent a fully randomized sample. A subtype analysis was not performed, and subtype response variance may also have affected results.

We found that there was a striking difference in results between the first 50% of patients enrolled and the second 50% of patients enrolled in trial 1, the only trial to evaluate this. In fact, if just the first 50% of patients were considered, there was a significant reduction in off time in the preladenant and rasagiline groups compared with the placebo group. Analyses did not suggest that this effect was because of site or regional influences. We hypothesize that the most likely explanation for this finding is that sites enrolled their most ideal patients first. After that, less ideal patients may have been enrolled to satisfy enrollment targets. That the second 50% was enrolled in half the time it took to enroll the first 50% raises concern that an enrollment push by the
sponsor or clinical research organization could potentially have degraded the quality of patients that sites were enrolling. These observations are consistent with results of an analysis of 4 phase 3 trials of paroxetine in major depression that found that a significant treatment effect was observed before approximately 100 patients had been enrolled per treatment arm.29 However, continuing to enroll additional patients (up to approximately 150) did not maintain the achieved level of significance and in one case turned a potentially positive study into a negative study. Notably, pooled analysis indicated that patients in the fourth quarter of enrollment were more likely to be placebo responders than early-enrolling patients.

Inclusion of an active control arm was useful to identify trial 1 as a failed trial. Rasagiline has several positive qualities as an active control. Although mild in efficacy and typically well tolerated, it has consistently reduced off time in adjunctive trials. However, exclusion of monoamine oxidase type B inhibitors in our phase 3 trials may have placed an additional burden on enrollment and made it harder for investigators to enroll ideal patients.

To adequately evaluate adjunctive PD medications, investigators must enroll appropriate patients and ensure rigorous diary education. Improved documentation of on and off states may be helpful, including UPDRS motor scores during testing, should be emphasized. Fourth, receiving reliable data is dependent on the patient completely and accurately completing the diary in a timely fashion. A telephone call to the patient the day before the diary is completed to remind him or her to complete the diary and to review good practice completion instructions may be helpful. Sites should also exercise discretion and not enroll patients who are likely to be poorly compliant in diary completion. Electronic diaries may be helpful to remind patients to complete entries on time and limit entries to 1 per period.
tronic diaries may improve results, although they have their own set of limitations to consider.30,31 There are also several objective motion sensors in development to assess PD throughout the day.32 However, they are limited in many respects, including distinction of sleep or rest from the off condition and inability to distinguish troublesome from nontroublesome dyskinesia.

The most important lessons we learned from these trials are listed in the Box.

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Huyck, Ho, Sklar, Rascal, and Michelson, and Hewitt.

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Conclusions
In our phase 3 trials, preladenant did not significantly reduce off time using essentially the same methods as in the phase 2b trial, in which efficacy was observed. However, we also did not observe a significant reduction in off time with the active control rasagiline, suggesting that our trials failed to adequately assess these medications.


