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Continued efficacy and safety of subcutaneous apomorphine in patients with advanced Parkinson's disease

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Abstract

The study purpose was to assess the efficacy of intermittent subcutaneous apomorphine (APO) as acute therapy for *off* episodes in advanced Parkinson's disease (PD) patients who had previously received APO for $\geqslant 3$ months. Patients ($n = 62$) were randomized to receive double-blind treatment with APO at their typically effective dose (TED; APO), APO at their TED + 0.2 mL (2.0 mg; APO + 2), placebo at volume equal to their TED (PL), or placebo at volume equal to their TED + 0.2 mL (PL + 2), for a single *off* episode. Significantly greater improvement in mean Unified PD rating scale motor scores was seen with pooled APO versus pooled placebo 20 min after administration (−24.2 vs. −7.4; $p < 0.0001$); the difference was also significant at 10 min ($p < 0.0001$). Overall adverse event incidence did not significantly differ between pooled APO and pooled PL. This study supports the long-term use of intermittent APO as effective acute therapy for *off* episodes in advanced PD patients.

Keywords: Intermittent subcutaneous apomorphine; Parkinson's disease; *off* episodes

1. Introduction

Approximately 1 million people in the United States (US) are estimated to have Parkinson's disease (PD), and about 50,000 new cases are diagnosed annually [1,2]. Within 5 years of diagnosis, approximately 40% of patients receiving levodopa begin experiencing motor fluctuations [3], most often *off* episodes occurring at the end of the oral anti-PD medication dosing interval ("end-of-dose wearing off") or at unpredictable times (spontaneous "on/off" episodes). A similar, or slightly lower, percentage develop dyskinesia [3]. *Off* episodes are characterized by both motor and non-motor features that may include hypomobility, freezing, reduced dexterity, panic attacks, pain, behavioral changes or autonomic dysfunction [4–6]. In advanced PD, *off* periods may be unpredictable and prolonged, at times lasting up to 5 h [7–9].

Therapeutic approaches used to manage *off* episodes include oral dopamine agonists, slow-release levodopa formulations, catechol-O-methyltransferase (COMT) inhibitors or monoamine oxidase inhibitors (MAOIs), increased levodopa dose frequency, and/or the addition of high-dose amantadine to the treatment regimen [10,11]. Despite optimum use of these strategies, complete control of motor fluctuations is seldom achieved.

Subcutaneous apomorphine (APO) was recently approved in the US for the acute intermittent treatment

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of *off* episodes associated with advanced PD, and has been shown in controlled clinical trials to be safe and highly effective in this indication [9,11,12–16]. No other agent currently available in the US has been shown to provide rapid efficacy in the acute treatment of *off* episodes.

The present study (APO302), one of the pivotal US registration studies for APO, assessed the efficacy of APO in patients who had already used APO for ⩾3 months. Patients with advanced PD may require long-term, acute management of *off* episodes, and therefore it is useful to evaluate, in the setting of a randomized, double-blind, placebo-controlled trial, the efficacy of APO in patients who have already been receiving this treatment chronically.

2. Methods

2.1. Study overview

This was a prospective, randomized, double-blind, placebo-controlled, parallel-groups study conducted at 26 US centers. PD patients on an optimal oral anti-PD regimen, who had been receiving acute intermittent APO therapy for *off* episodes for ⩾3 months before study enrollment, received a single dose of APO or placebo. The protocol was approved by the institutional review boards of participating centers. The study was performed in accordance with the revised Declaration of Helsinki. All subjects provided written informed consent.

2.2. Patients

All patients were drawn from and were concurrently participating in a larger multicenter open-label US safety study of APO. All were >18 years of age with Hoehn and Yahr stage II–IV, and experienced *off* episodes despite an optimal oral anti-PD regimen (including carbidopa/levodopa plus ⩾1 oral dopamine agonist for ⩾30 days before randomization).

Patients had received a prescribed APO regimen for ⩾3 months, and were receiving ⩾2 APO doses/day in the week before enrollment. They were required to complete two visits: a pre-study/baseline visit and a treatment day visit; study exit assessments occurred at the end of the treatment day visit (Fig. 1).

Exclusion criteria for this study were identical to those of the larger concurrent safety study in which all subjects participated, and included patients under medical therapy for clinically significant psychoses or dementia not related to their anti-PD medications; patients with unstable and clinically significant disease of the cardiovascular, hematologic, hepatic, renal, metabolic, respiratory, gastrointestinal or endocrinological systems; and patients allergic to morphine or its derivatives, sulfur, sulfur-containing medication, sulfites, sulfates, or trimethobenzamide.

2.3. Treatments

On the treatment day visit, patients took their standard morning oral anti-PD medications and reported to the center to await the next *off* episode. No other anti-PD medications were allowed during the evaluation period. Test medication was given after the onset of the first *off* episode occurring ⩾1 h after the patient's morning dose of oral anti-PD medications. Patients were randomized in a 2:2:1:1 ratio to one of four groups (Fig. 1): (i) APO at their typically effective dose (APO); (ii) APO at their typically effective dose + 0.2 mL (2.0 mg) (APO + 2); (iii) placebo at volume equal to their typically effective dose (PL); (iv) or placebo at volume equal to their typically effective dose + 0.2 mL (PL + 2). Patients had undergone dose titration during the open-label safety study in which they were concurrently participating, with subsequent dose adjustments permitted. The APO typically effective dose was the dose of APO that had been effective in treating *off* episodes during the last 3 months prior to participation in the APO302 study; this ranged from 0.15 to 1.0 mL/dose (1.5–10.0 mg/dose).

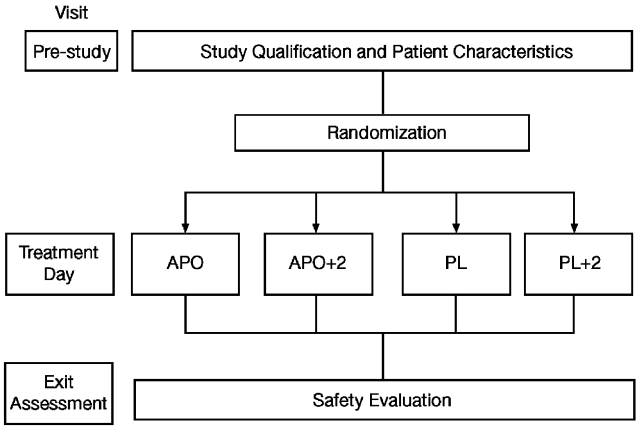

Fig. 1. APO302 study design.

The maximum allowed dose was 1.0 mL (10.0 mg) as a single injection or 50 mg as a daily dose. The APO + 2 group was included to evaluate the tolerability of excess drug administration, and to determine whether patients receiving long-term APO experienced attenuation of effectiveness requiring a higher dose of APO to achieve rescue from *off* episodes.

Apomorphine hydrochloride 10 mg/mL (Mylan Bertek Pharmaceuticals Inc, Research Triangle Park, NC) or matching placebo was supplied in 2 mL ampules. Kit assignments and numbers were obtained by random number generation and were issued to investigators in blocks of six by an independent packaging contractor. Investigators assigned each patient to a kit in sequential numeric order and administered a single dose of study drug per kit instructions after the onset of the first *off* episode. Research staff and patients remained blinded until the last patient completed the study and data were analyzed.

2.4. Evaluations

All assessments were performed by qualified staff. The first assessment took place after the onset of an *off* episode, but before APO or placebo administration (pre-dose); subsequent assessments were performed at various time points (post-dose) up to 90 min after administration (Table 1). The presence of the "off" state was determined by the investigator's assessment

Table 1
Study assessments

	Time post-dose (min)								
	Pre-dose	2.5	5	7.5	10	15	20	40	90
Perception of onset of treatment effect	X	X	X	X	X	X	X	X	
WSST	X	X	X	X	X	X	X	X	
UPDRS motor score	X				X		X		X
Dyskinesia assessment	X				X		X		X
Orthostatic monitoring with ECG	X						X		X
Adverse event assessment	X				X		X		X

that the patient was "off" and that a significant degree of immobility was present, with the intent to administer the APO when the nadir with respect to immobility had been reached.

2.4.1. Efficacy

The primary efficacy variable was the change in Unified Parkinson's Disease Rating Scale (UPDRS) motor score 20 min post-dose. Secondary efficacy measures included change in UPDRS motor scores at 10 and 90 min, and percent change in UPDRS motor scores at 10, 20 and 90 min.

The onset of APO action was assessed using the Webster step-seconds test (WSST) [17], modified to allow completion of each assessment within 60 s. The patient began in a sitting position, and was asked to stand, walk, turn around, walk back and sit. The number of steps taken with the right foot per round trip of 15 feet out plus 15 feet back, and the time taken to accomplish the task, were recorded. The test was modified to allow a total evaluation time of 60 s; if a patient reached the 60 s cutoff point without completing the walking distance, the test was stopped and 60 s was recorded in the appropriate field on the workbook. If the patient was unable to complete the test within the 60 s timeframe, an imputed score of 9999 was recorded (lower scores indicating a better result). The WSST was performed pre-dose and at 2.5, 5, 7.5, 10, 15, 20 and 40 min following APO injection.

Dyskinesias were assessed using a 4-point rating scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe). A more formal dyskinesia rating scale was not employed in order to economize assessment time. Participants' assessments of the time of onset of treatment effect were determined by asking them to state the time at which they perceived improvement in their mobility.

2.4.2. Safety

Safety assessments included: (i) recording of the incidence of adverse events (AEs) after dosing; (ii) changes in orthostatic monitoring values (pulse, systolic and diastolic blood pressures (BP)) from pre-dose to 20 and 90 min after dosing; (iii) change in ECG values (atrial rate, ventricular rate, PR, RR, QRS, QT and corrected QT (QTc)) from pre-dose to 20 and 90 min after dosing; (iv) incidence of symptomatic orthostatic change and orthostatic hypotension (Criterion 1: a drop of $\geqslant$20 mmHg in systolic BP (SBP) or $\geqslant$10 mmHg in diastolic BP (DBP); Criterion 2: a drop of $\geqslant$30 mmHg in SBP to a standing value $\leqslant$90 mmHg; or a $\geqslant$20 mmHg drop in DBP to a standing value $\leqslant$50 mmHg). BP measurements were performed in the sitting and standing positions. A 5-min acclimation period in the sitting position prior to measurement was employed; standing measurements were recorded after 2 min of standing. AEs were categorized by investigators for duration, severity, and possible relation to the study drug.

2.5. Statistical analyses

2.5.1. Sample size

Two previous studies of APO indicated mean (standard deviation) changes in UPDRS score of −0.11 (5.74) and −5.50 (15.00) for placebo versus −23.85 (5.74) and −19.40 (15.00) for APO [9,18]. Sample size calculations were therefore carried out using estimated means (standard deviations) of −5 (14) for placebo and −20 (14) for APO. Given a significance level of 0.05, a sample size of 20 patients for placebo and 40 for APO would provide 97% power to detect a difference of 15 in the change in UPDRS scores.

2.5.2. Study populations

Both the safety and intent to treat (ITT) analysis included all randomized participants who received APO or placebo on the treatment day visit.

2.5.3. Efficacy analyses

The primary efficacy variable was analyzed based on an analysis of covariance (ANCOVA). All four treatments were in the model (APO, APO + 2, PL, PL + 2). The primary contrast was the pooled PL treatment groups (pooled PL) versus pooled APO treatment groups (pooled APO). Analyses of covariance were also employed for evaluations of UPDRS motor scores from pre-dose to 10 and 90 min after treatment and percent change in UPDRS motor scores from pre-dose to 10, 20, and 90 min. Changes in dyskinesia assessment and WSST scores at each time point were assessed by a non-parametric ANCOVA comparing pooled APO and pooled PL data. The time (in minutes) from injection to patient-declared onset of relief was analyzed using the Wilcoxon rank sum test; a survival analysis was also performed using the log rank test. The accepted level for statistical significance in all efficacy evaluations was 5% ($p = 0.05$) (two-sided tests).

2.5.4. Safety

The incidence of AEs was compared between treatment groups using a chi square analysis.

Changes in orthostatic monitoring values and ECG values from pre-dose to 20 and 90 min post-dosing were evaluated using ANCOVA. The incidence of symptomatic orthostatic change and orthostatic hypotension was compared across treatment groups using chi square analysis. Safety analyses used a 10% ($\alpha = 0.10$) significance level as a descriptive guide.

3. Results

3.1. Patients

Patients were recruited between July 2001 and June 2002. All 62 enrolled patients were included in both ITT and safety analyses. Two patients assigned to the PL group found their unrelieved *off* episodes to be intolerable, and discontinued the study at 20 and 50 min post-placebo dose (Fig. 2); however, they did contribute to the efficacy data.

Table 2 shows baseline demographics and clinical characteristics. The different groups were generally well matched with no statistically significant differences in baseline characteristics. On average, patients had used APO for 14.5 months before enrollment.

3.2. Efficacy

3.2.1. UPDRS motor scores

There was no significant difference between the PL and PL + 2 groups in the change in mean UPDRS motor score at 20 min (Table 3); therefore data from the pooled PL group were used for comparison. The APO and APO + 2 groups showed significantly improved UPDRS motor scores at 10 and 20 min compared with pooled PL (Fig. 3, Table 3).

Significantly superior improvement was seen for pooled APO compared to pooled PL on the primary comparison of mean change in UPDRS motor scores 20 min after dosing (−24.2 vs. −7.4; $p < 0.0001$), and also at 10 min (−19.9 vs. −5.6; $p < 0.0001$), but not 90 min ($p = 0.8558$) (Fig. 3, Table 3). Pooled APO was significantly superior to pooled PL with respect to percent changes in UPDRS motor scores from pre-dose to 10 min (−48.9% vs. −19.3%; $p < 0.0001$) and 20 min (−58.7% vs. 24.1%; $p < 0.0001$), but not 90 min ($p = 0.9031$).

The APO + 2 group had only slightly greater improvement in UPDRS motor scores than the APO group at 10 min post-dose; the level of improvement was similar in both groups at 20 min (Fig. 3).

3.2.2. WSST score

WSST results were not normally distributed and were analyzed by non-parametric ANCOVA. Significant improvement of pooled APO over pooled PL in median change from pre-dose WSST was seen at 7.5 min (−269.5 vs. −58.0; $p = 0.0230$), 10 min (−400.5 vs. −78.0; $p = 0.0050$), 15 min (−426.5 vs. −66.0; $p = 0.0005$), 20 min (−462.5 vs. −39.9; $p < 0.0001$) and 40 min (−445.0 vs.−62.5; $p = 0.0004$).

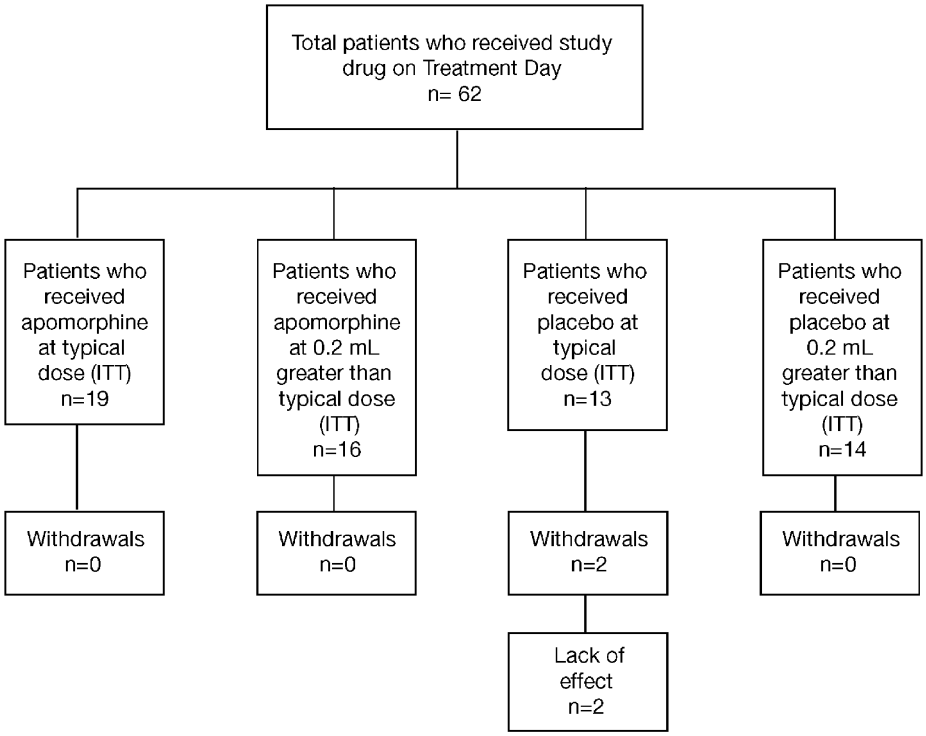

Fig. 2. Patient disposition.

Table 2
Baseline demographic and clinical characteristics[a]

Characteristic	Total ($n = 62$)	Pooled APO ($n = 35$)	APO ($n = 19$)	APO + 2 ($n = 16$)	Pooled PL ($n = 27$)	PL ($n = 13$)	PL + 2 ($n = 14$)	p-value[b]
Gender n (%)								
Male	45 (72.6)	25 (71.4%)	15 (78.9%)	10 (62.5)	20 (74.1)	8 (61.5)	12 (85.7)	1.00
Female	17 (27.4)	10 (28.6%)	4 (21.1%)	6 (37.5)	7 (25.9)	5 (38.5)	2 (14.3)	
Ethnicity n (%)								
Caucasian	60 (96.8)				25 (92.6)	11 (84.6)	14 (100)	0.1856
Hispanic	1 (1.6)	35 (100)	19 (100)	16 (100)	1 (3.7)	1 (7.7)		
Asian	1 (1.6)				1 (3.7)	1 (7.7)		
Age, years	65.5 (±1.2)	64.8 (±1.5)	64.0 (±2.1)	65.7 (±2.3)	66.5 (±1.9)	66.9 (±3.0)	66.2 (±2.5)	0.4709
Age at onset of PD, years	50.8 (±1.4)	51.1 (±1.4)	51.6 (±1.8)	50.6 (±2.3)	50.4 (±2.6)	49.1 (±3.9)	51.7 (±3.6)	0.8057
Days on apomorphine	434 (±23)	426 (±32)	369 (±41)	493 (±46)	444 (±32)	469 (±52)	421 (±40)	0.6901
Typically effective apomorphine dose (mg)	3.82 (±0.23)	4.2 (±0.32)	4.59 (±0.48)	3.75 (±0.39)	3.32 (±0.30)	3.38 (±0.55)	3.26 (±0.29)	0.0532
Baseline "on" UPDRS motor score[c]	22.89 (±1.6)	25.65 (±2.09)	26.44 (±2.90)	24.75 (±3.09)	19.41 (±2.38)	22.62 (±3.80)	16.43 (±2.85)	0.0531

Abbreviations: APO, subcutaneous apomorphine; PL, placebo; UPDRS, Unified Parkinson's disease rating scale.
[a]Data are given as mean (±SEM) for the ITT population unless otherwise indicated.
[b]The p-value for pooled APO versus pooled PL using Fisher's exact test for categorical variables and ANCOVA for continuous variables.
[c]One patient in the APO group was excluded from the analysis because the assessment could not be made during an "on" period.

3.2.3. Subjective assessment of time to onset of action

Patients' perceptions of a significant improvement in mobility indicated a mean time to onset of action of 7.26 min for pooled APO versus 11.44 min for pooled PL ($p = 0.0058$, log-rank test).

3.2.4. Dyskinesia assessment

Patients who received APO had significant increases in dyskinesia scores compared with PL 10 and 20 min after dosing ($p = 0.0021$ and $p < 0.0001$, respectively), but not at 90 min ($p = 0.2536$).

3.3. Safety

3.3.1. Adverse events

There were no deaths or other serious AEs during this single-day study. Twenty-five of 62 (40.3%) patients experienced ⩾1 adverse event; all AEs were of mild or moderate intensity. There was no significant difference in the overall incidence of AEs between pooled APO and pooled PL (45.7% vs. 33.3%; $p = 0.3284$). The incidence of AEs occurring in >1 patient receiving APO is shown in Table 4. The most common treatment-related treatment-emergent AEs in the pooled APO group were yawning (22.9%), somnolence (17.1%), dizziness (11.4%), rhinorrhea (8.6%) and nausea (5.7%).

Overall AE rates in the APO and APO + 2 groups were 42.1% and 50.0%, respectively (Table 4). There was a slight, but statistically significant, increase in the rate of AEs in the APO + 2 group versus pooled PL at 10 min post-dose ($p = 0.0925$). No patients receiving their typically effective dose of APO reported nausea or rhinorrhea—AEs commonly associated with APO.

3.3.2. Pulse rates and blood pressure

APO decreased pulse and BP in a dose-dependent manner. Small but statistically significant differences in the mean change from predose in sitting pulse were seen at 20 min between pooled PL (+1.2 bpm) and pooled APO (−3.4 bpm; $p = 0.0450$) or APO + 2 (−6.1 bpm; $p = 0.0105$), but not the APO group (−1.1 bpm; $p = 0.4738$).

There were significantly greater mean reductions from predose for sitting SBP (−10.9 vs. +4.6 mmHg; $p = 0.0021$) and standing SBP (−14.1 vs. −0.8 mmHg; $p = 0.0066$) at 20 min for pooled APO versus pooled PL. There were small, but statistically significant, decreases in sitting DBP (−3.4 vs. +0.7 mmHg; $p = 0.0681$) and standing DBP (−4.2 vs. −0.3 mmHg; $p = 0.0481$) for pooled APO versus pooled PL at 20 min. Differences in BP reduction tended to be greater between APO + 2 and pooled PL than between APO and pooled PL, at 20 and 90 min. No significant differences were observed between any of the APO groups versus pooled PL at 90 min.

Table 3
p-Values reflecting mean change in UPDRS motor scores from pre-dose across all time points

Treatment group	10 min	20 min	90 min
p-values versus pooled PL			
Pooled APO	<0.0001	<0.0001[a]	0.8558
APO	0.0003	<0.0001	0.9608
APO + 2	<0.0001	<0.0001	0.8034
p-values vs. PL			
APO	0.0052	<0.0001	0.8751
p-values vs. PL + 2			
APO + 2	<0.0001	<0.0001	0.9202
p-values vs. PL + 2			
PL	0.5412	0.7742	0.8307

The *p*-values are based on estimate statement in ANCOVA.
[a]Primary efficacy endpoint.

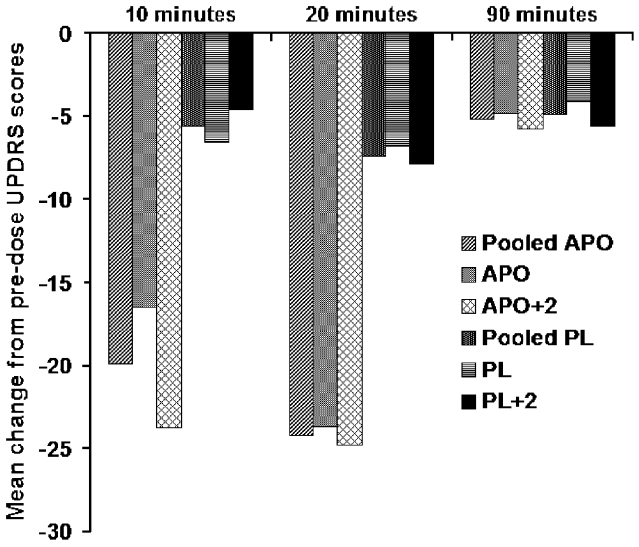

Fig. 3. Mean changes in UPDRS motor score: all time points.

3.3.3. Orthostatic hypotension and symptomatic change

Although there were differences between pooled APO and pooled PL in individual orthostatic monitoring parameters, there were no differences in the incidence of orthostatic hypotension by Criterion 1 for pooled APO versus pooled PL at 20 or 90 min ($p = 0.2505$ and $p = 0.1657$, respectively). Nineteen patients (pooled APO: 11; pooled PL: 8) had BP measurements that met Criterion 1 for orthostatic hypotension. Six of the patients with orthostasis (pooled APO: 5; pooled PL: 1) experienced events at both a pre-dose and post-dose assessment. Eight patients exhibited orthostasis only at a post-dose assessment (pooled APO: 3; pooled PL: 5). Five patients experienced orthostasis only during the pre-dose period (pooled APO: 3; pooled PL: 2). No patient exhibited post-dose orthostasis based on Criterion 2.

There was no increase in orthostasis in the APO and APO + 2 groups compared with pooled PL. There was no significant difference between pooled APO and pooled PL in symptomatic change at 20 and 90 min.

3.3.4. ECG

There was a statistically significant increase from pre-dose in the QT and RR intervals at 20 min for pooled APO compared to pooled PL ($p = 0.0438$ and $p = 0.0517$, respectively). RR was significantly increased at 90 min ($p = 0.0566$). At 20 min post-dose, QTc was 6 ms longer for pooled APO versus pooled PL ($p = 0.3577$). At 20 min, the mean change from predose in QTc was 4 ms longer for pooled APO versus pooled PL; this difference was not significant ($p = 0.4157$).

Comparison of the APO and APO + 2 groups showed no relationship between APO dose and change from pre-dose in QTc. Three patients (1 each for APO + 2, APO and PL) had ECG abnormalities (sinus tachycardia, atrial flutter, and premature ventricular ectopic beats, respectively). None of these patients discontinued treatment.

4. Discussion

For those PD patients who, despite being optimally managed with currently available medications (including dopamine agonists and COMT inhibitors), continue to experience *off* episodes, subcutaneous APO is effective as an intermittent acute treatment. In this study involving patients who had already used APO for $\geqslant 3$ months, there was an improvement of approximately 59% in UPDRS motor scores at 20 min after dosing with APO.

APO significantly improved patient mobility versus placebo as early as 7.5 min, demonstrating that APO provides very rapid relief from *off* symptoms, and

Table 4
Incidence of treatment-emergent treatment-related adverse events

	APO ($n = 19$)		APO + 2 ($n = 16$)		Pooled APO ($n = 35$)		Pooled PL ($n = 27$)	
	n	%	*n*	%	*n*	%	*n*	%
Any adverse event	8	42.1	8	50.0	16	45.7	9	33.3
Yawning	3	15.8	5	31.3	8	22.9	2	7.4
Somnolence	3	15.8	3	18.8	6	17.1	0	0
Dizziness[a]	2	10.5	2	12.5	4	11.4	1	3.7
Rhinorrhea	0	0	3	18.8	3	8.6	0	0
Nausea	0	0	2	12.5	2	5.7	0	0

Events listed are those that occurred in more than one patient receiving apomorphine.
[a]Excluding vertigo.

improvement persisted for at least 40 min after dosing. The WSST and patients' subjective assessment of onset of action showed rapidly improved mobility that paralleled the time course of changes in UPDRS motor score. The fast onset observed with APO in this study is consistent with earlier short-term trials showing rapid relief from symptoms [12,15], indicating that long-term intermittent APO treatment does not result in an increased latency period between administration and the onset of relief.

Study results suggested no tachyphylaxis. Once the patient's typically effective APO dose was established, there was no significant advantage, in terms of magnitude of response as measured by UPDRS, in exceeding that established dose $\geqslant 3$ months later. Indeed, increasing the dose of APO by 0.2 mL (2.0 mg) resulted in increased AEs without providing any substantial efficacy benefit. These findings indicate that intermittent APO provides patients experiencing *off* episodes with symptomatic improvement even after using this treatment for an extended period. The current study, in which the mean duration of previous APO exposure was >1 year, expands on the findings of previous studies [14,19], in the setting of a randomized, double-blind, placebo-controlled trial.

The present results document the safety of intermittent APO in patients with PD. There was no statistically significant difference in the overall incidence of AEs between APO and placebo. The safety and tolerability observed with APO in this trial is consistent with other reports, demonstrating that APO administered intermittently over long intervals is safe and well tolerated by patients with PD [14,19].

The similarities between the groups in the proportion of patients with orthostasis overall, and the proportion with orthostasis observed only at a post-dose assessment, suggest that ongoing administration of intermittent APO did not worsen the incidence of orthostasis.

APO has previously been shown to reduce resting SBP and DBP, and therefore has the potential to exacerbate coronary (and cerebral) ischemia, as noted in the prescribing information [20]. In the present study, sitting and standing SBP and DBP were significantly lower for pooled APO compared to pooled PL 20 min after dosing, but there were no significant increases in cardiovascular disorders compared to pooled PL, and no reports of syncope or postural dizziness, in either APO group. However, it should be noted that the US prescribing information for APO advises caution in prescribing APO for patients with known cardiovascular and cerebrovascular disease or who develop such symptoms [20].

In conclusion, the results of this study show that intermittent APO is effective after long-term use ($\geqslant 3$ months) for the acute treatment of *off* episodes associated with advanced PD.

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