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Long-term safety and efficacy of apomorphine infusion in Parkinson's disease patients with persistent motor fluctuations: Results of the open-label phase of the TOLEDO study

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ABSTRACT

Introduction: The randomized, double-blind phase (DBP) of the TOLEDO study confirmed the efficacy of apomorphine infusion (APO) in reducing OFF time in PD patients with persistent motor fluctuations despite optimized oral/transdermal therapy. Here we report safety and efficacy results including the 52-week open-label phase (OLP).

Methods: All patients completing the 12-week DBP (including those switching early to open-label treatment) were offered OLP entry. The primary objective was the evaluation of long-term safety of APO.

Results: Eighty-four patients entered the OLP (40 previously on APO, 44 on placebo) and 59 patients (70.2%) completed the study. The safety profile of APO was consistent with experience from extensive clinical use. Common treatment-related adverse events (AEs) were mild or moderate infusion site nodules, somnolence and nausea. Fourteen (16.7%) patients discontinued the OLP due to AEs, those involving >1 patient were infusion site reactions (n = 4) and fatigue (n = 2); hemolytic anemia occurred in one case. Reduction in daily OFF time and improvement in ON time without troublesome dyskinesia were sustained for up to 64 weeks. Pooled data for week 64 (n = 55) showed a mean (SD) change from DBP baseline in daily OFF time of −3.66 (2.72) hours and in ON time without troublesome dyskinesia of 3.31 (3.12) hours. Mean (±SD) daily levodopa-equivalent dose decreased from DBP baseline to week 64 by 543 mg (±674) and levodopa dose by 273 mg (±515).

Conclusions: The safety and efficacy of APO infusion were demonstrated with long-term use for persistent motor fluctuations, allowing substantial reductions in oral PD medication.

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1. Introduction

In Parkinson's disease (PD), many of the motor symptoms typically respond well to dopaminergic treatment. However, with continuing neurodegeneration, the majority of patients develop motor fluctuations and dyskinesias. In patients where these motor complications can no longer be well controlled by oral medication, subcutaneous infusion of the dopamine agonist apomorphine (APO) offers continuous drug delivery and has been used in clinical practice around the world for many years. Its efficacy and tolerability have been observed in numerous open-label studies [1–5].

The TOLEDO study is the first prospective, randomized, placebo-controlled trial (RCT) to investigate the efficacy and safety of APO infusion in PD patients. Results of the 12-week double-blind phase (DBP) of TOLEDO confirmed that, in PD patients who have persistent motor fluctuations despite optimized oral/transdermal therapy, APO treatment leads to a marked and significant improvement in OFF time, which is associated with a clinically meaningful improvement in ON time without troublesome dyskinesias [6].

The clinical benefits and tolerability of APO have been shown to be sustained with long-term use in observational studies [7–13]. Here we report the long-term safety and efficacy results of those patients who continued in the 52-week open-label phase (OLP) of the TOLEDO study.

2. Methods

The design and conduct of the TOLEDO study (NCT02006121) have been reported previously [6].

All patients who completed the 12-week DBP were offered entry into the OLP to receive APO for 52 weeks. The cohort who entered the OLP also included patients who switched early from the DBP due to lack of efficacy of the blinded study drug. Patients entering the OLP and investigators remained blinded to the original treatment assignments during the DBP. In order to preserve blinding, all patients entering the OLP were re-titrated onto APO infusion, starting at a flow rate of 1 mg/h, until they reached their individually effective and well-tolerated dose. Subsequent treatment, including daily duration of infusion, and any further adjustments to the APO flow rate and concomitant oral medication, were carried out according to local standards.

OLP study visits occurred at 12, 24, 36, and 52 weeks from the end of the DBP, with additional telephone contacts at weeks 6, 18, 30 and 44 to record any changes in concomitant diseases or medication and any adverse events (AEs) experienced since the previous visit.

Safety assessments included evaluation of vital signs, AEs, changes in local tolerability at the infusion site, clinical laboratory variables, Questionnaire for Impulsive–Compulsive Disorders in PD (QUIP; long version) [14], Epworth Sleepiness Scale (ESS) [15], and the Columbia Suicide Severity Rating Scale (C-SSRS) [16].

As in the DBP, patients continued to complete the 24-h home diary assessment of motor status at 30-min intervals over 2 days before each visit, recording periods when they were ON without dyskinesia, without troublesome dyskinesia or with troublesome dyskinesia, OFF, and sleeping.

Other efficacy parameters collected included Patient Global Impression of Change (PGIC), change in MDS-UPDRS Part III (motor examination) scores during ON periods, change in combined scores for 4.3 (time spent in OFF) and 4.4 (functional impact of fluctuations) of MDS-UDPRS Part IV, and change in quality of life (QoL) assessed using the 8-item Parkinson's Disease Questionnaire (PDQ-8) [17]. Changes in oral levodopa and levodopa-equivalent dose (LED) [18] were also assessed.

All analyses for the OLP phase of the study were conducted on the OLP safety population, which was defined as all patients who received at least one dose of APO in the OLP.

TOLEDO was conducted in accordance with the International Conference on Harmonization Good Clinical Practice guidelines and the Declaration of Helsinki. Before starting the study, the study protocol, patient information sheet, and informed consent form were approved by the independent ethics committees and the competent regulatory authorities in accordance with local legal requirements in each participating country. All patients completed an informed consent form on entering the study and again when entering the OLP.

3. Results

3.1. Patients

The first patient was enrolled into the DBP on 03 March 2014 and the last patient completed the OLP on 08 Jun 2017. Eighty-four patients entered the OLP, including 16 placebo-treated patients who switched early from the DBP (all due to lack of efficacy) and two APO-treated patients who switched early from the DBP (one due to lack of efficacy and the other due to an inability to tolerate the minimum target infusion rate of 3 mg/h; this patient continued to the end of the OLP at a dose of 1.0–1.5 mg/h). Mean (SD) daily duration of infusion at the end of the DBP for the cohort of patients who entered the OLP (n = 84) was 13.19 (2.99) hours (95% CI: 12.54, 13.84). Of the OLP subjects, 40 had previously been treated with APO during the DBP (APO/APO) and 44 with placebo (PBO/APO). Fifty-nine patients (70.2%) completed the study (30 APO/APO and 29 PBO/APO) (Fig. 1).

The mean (SD) age of study patients in the OLP safety population (n = 84) was 64.3 (8.2) years with a mean (SD) disease duration of 10.9 (5.0) years.

The mean (SD) infusion rate of apomorphine during the OLP was 4.45 (1.41) mg/hour for APO/APO patients, 4.71 (1.73) mg/hour for PBO/APO patients, and 4.57 (1.58) mg/hour for all patients combined. The maximum infusion rate used was 9 mg/h. The median duration of APO treatment was 52.1 weeks (quartile 1: 32.8, quartile 3: 53.1).

3.2. Combined safety results

An overall summary of AEs occurring from DBP baseline to the end of the OLP is shown in Table 1 for the combined OLP safety set (n = 84). No deaths occurred during the study and there were no serious unexpected AEs. The vast majority of AEs reported were classified as mild to moderate.

Patients who switched to APO in the OLP had AE profiles similar to those experienced by APO-treated patients in the DBP. The most common treatment-related AEs were mild or moderate infusion site reactions, somnolence and nausea. A total of 38 patients experienced infusion site nodules; the first event was reported a median of 10 days from the first apomorphine infusion treatment and the median duration of an individual event was 109 days. The apomorphine dose remained unchanged in 57/89 (64%) of cases, and in approximately 75% of cases the skin nodules had either resolved or were resolving when the patient completed the trial.

Fourteen (16.7%) patients discontinued the OLP due to AEs; only infusion site reactions (n = 4) and fatigue (n = 2) occurred in more than one patient; the remainder of AEs resulting in discontinuation were varied and involved a single patient in each case.

The overall incidence of patients with at least one AE in the OLP safety set was 97.5% for APO/APO patients and 100% for PBO/APO patients. In the OLP safety set, AEs leading to dose modification at any point during the study occurred in 65% of APO/APO patients and in 54.5% of PBO/APO. The incidence of new AEs overall, including those related to study medication, decreased throughout the duration of the OLP of the study. Mean time to the last occurrence of an AE while receiving treatment was 30.7 weeks (95% CI: 26.4, 35.0).

Mean (SD) ESS scores increased from 7.8 (4.3) at DBP baseline to 10.8 (4.9) at week 64 for APO/APO patients, 8.5 (5.8) at DBP baseline to 10.6 (5.9) at week 64 for PBO/APO patients, and 8.1 (5.1) at DBP baseline to 10.7 (5.4) at week 64 for all these patients combined.

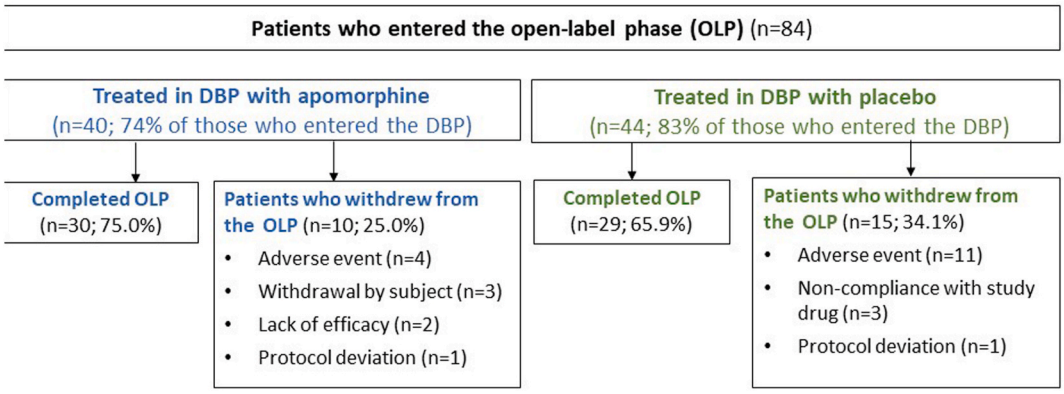

Fig. 1. Patient flow through the TOLEDO study OLP.

Table 1
Combined safety results for all patients entering the OLP measured from DBP baseline.

OLP safety set (n = 84)	n (%)			
Patients with at least one AE	83 (98.8%)			
AEs related to the study medication	77 (91.7%)			
Serious treatment-related AEs	8 (9.5%)			
Severe treatment-related AEs	13 (15.5%)			
AEs leading to study discontinuation:	14 (16.7%)			
• Infusion site reactions	4 (4.8%)			
• Fatigue	2 (2.4%)			
• Autoimmune hemolytic anemia	1 (1.2%)			
• Delirium	1 (1.2%)			
• Dementia	1 (1.2%)			
• Disturbance in attention	1 (1.2%)			
• Lymphoma	1 (1.2%)			
• Nausea	1 (1.2%)			
• Panic attack	1 (1.2%)			
• Somnolence	1 (1.2%)			
AEs with a local intolerability (skin changes at injection site)	60 (71.4%)			
Most common AEs (≥10% frequency)	Mild	Moderate	Severe	Total
• Infusion site nodules	38 (45.2%)	8 (9.5%)	–	46 (54.8%)
• Nausea	14 (16.7%)	5 (6.0%)	–	19 (22.6%)
• Somnolence	7 (8.3%)	10 (11.9%)	2 (2.4%)	19 (22.6%)
• Dyskinesia	7 (8.3%)	6 (7.1%)	1 (1.2%)	14 (16.7%)
• Fall	10 (11.9%)	3 (3.6%)	1 (1.2%)	14 (16.7%)
• Insomnia	7 (8.3%)	6 (7.1%)	–	13 (15.5%)
• Constipation	8 (9.5%)	3 (3.6%)	1 (1.2%)	12 (14.3%)
• Dizziness	11 (13.1%)	–	–	11 (13.1%)
• Infusion site erythema	8 (9.5%)	2 (2.4%)	1 (1.2%)	11 (13.1%)
• Headache	7 (8.3%)	2 (2.4%)	–	9 (10.7%)

DBP, double-blind phase; OLP, open-label phase.

There were no changes throughout the study in QUIP or C-SSRS scores. In eight patients, behaviors related to increased impulsivity (ten incidents) were reported; all were rated as mild, three resolved and none led to study discontinuation: four cases of punding (one resolved, one outcome unknown, two not resolved), four cases of hypersexuality (two resolved, two not resolved), and two cases of overeating (not resolved).

The vast majority of laboratory results outside the normal range were considered not clinically relevant. One case of autoimmune hemolytic anemia occurred in a 79-year-old female patient after 55 weeks of APO treatment. The onset was sub-acute, and the patient made a full recovery on discontinuing APO and receiving treatment with blood transfusions and corticosteroids.

There was a reduction in systolic blood pressure noted for all patients from a mean (SD) of 132.2 (17.6) mm Hg at DBP baseline to a mean of 120.3 (14.1) mm Hg at week 64; changes for diastolic blood pressure were from 77.8 (9.6) mm Hg to 75.3 (10.5) mm Hg. Five instances of orthostatic hypotension were reported as AEs in the OLP cohort (three of mild severity, two moderate; four resolved, one unknown outcome); none led to study discontinuation. No ECG findings resulted in study discontinuation and no cases of clinically-relevant QTc prolongation were observed.

3.3. Change in daily OFF time

The change in daily OFF time from DBP baseline to the end of the OLP is shown in Fig. 2. Mean (SD) daily OFF time at DBP baseline was 6.7 (2.3) hours for the APO/APO patients, 7.0 (2.7) hours for PBO/APO patients, and 6.9 (2.5) hours for all these patients combined. On switching to APO in the OLP, PBO/APO patients reached the same level as the APO/APO group. At week 24 (after 12 weeks of OLP treatment), the mean (SD) change in daily OFF hours from DBP baseline for all patients treated with APO in the OLP (n = 55) was −3.14 (3.25) hours. For the remainder of the OLP, patients experienced further improvements reaching mean (SD) daily OFF time at week 64 (after 52 weeks of OLP treatment) of −3.66 (2.72) hours.

3.4. Change in daily ON time without troublesome dyskinesia

The mean (SD) daily duration of ON time without troublesome dyskinesia (OWTD) at DBP baseline was 8.4 (2.3) hours for APO/APO patients, 8.5 (2.6) hours for PBO/APO patients, and 8.4 (2.4) for all these patients combined. The change in daily OWTD time from DBP baseline to the end of the OLP is shown in Fig. 3. Once PBO/APO patients switched to APO in the OLP, they also experienced an improvement in OWTD, mirroring the results for OFF time and reaching the same level as the APO/APO group. At week 24, the mean (SD) change in OWTD from DBP baseline for all patients treated with APO in the OLP was 2.82 (3.11) hours. For the remainder of the OLP, patients experienced modest further improvements in OWTD, reaching a mean (SD) of 3.31 (3.12) hours at week 64.

3.5. ON time with troublesome dyskinesia

Although recorded in the patients' home diaries, the study was not powered to detect significant differences in ON time with troublesome

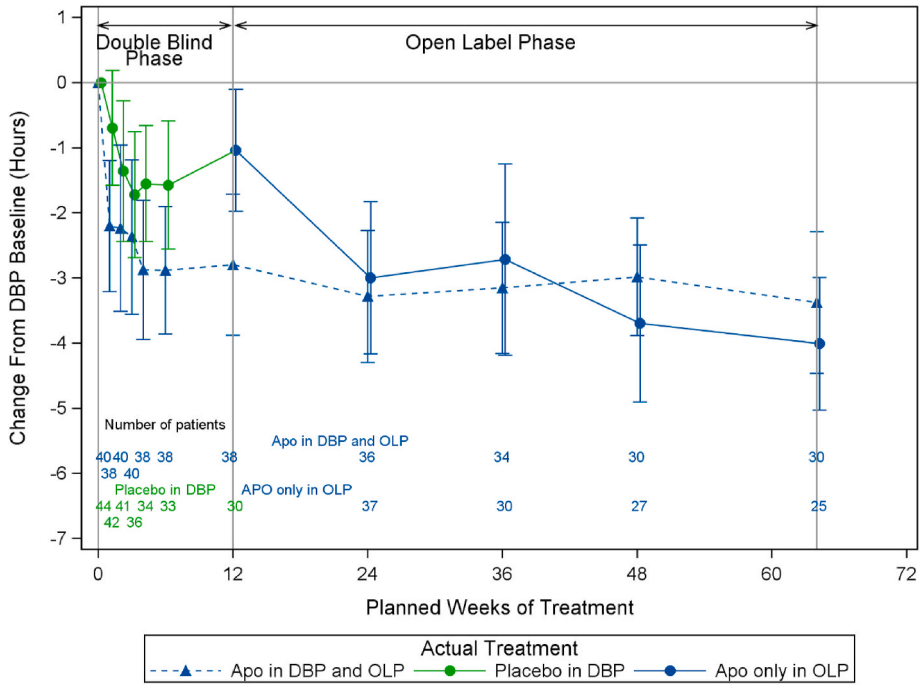

Fig. 2. Changes from DBP baseline in daily OFF time over 24 h (OLP safety set, n = 84).

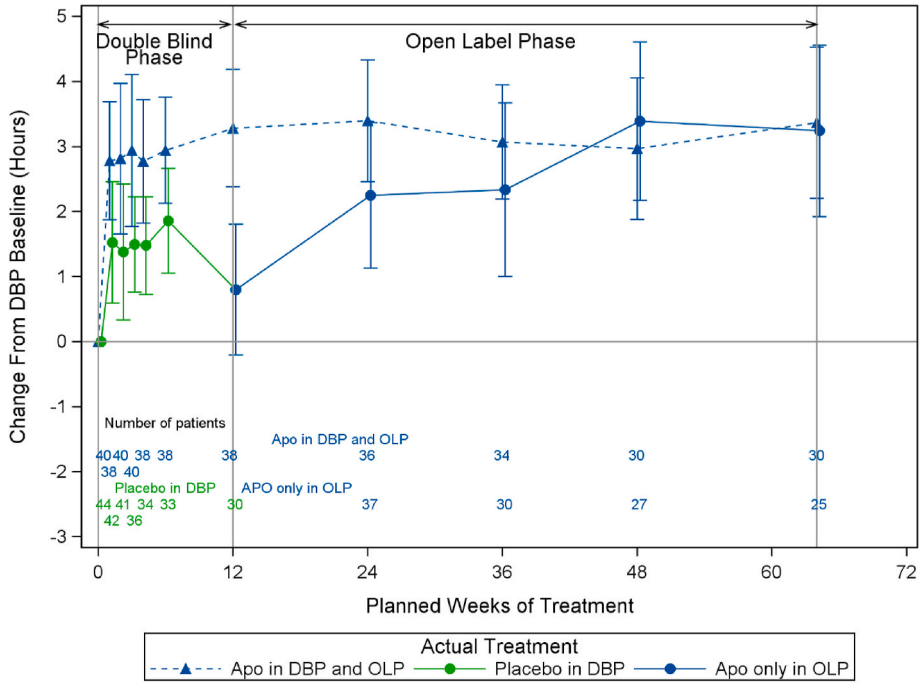

Fig. 3. Changes from DBP baseline in daily ON time without troublesome dyskinesia (OLP safety set; n = 84).

dyskinesia. Mean (SD) values at baseline in the OLP safety set (n = 84) were 1.16 (1.68) hours (95% CI: 0.80, 1.53) and at the final follow-up (the last observation before study completion or withdrawal) (n = 84) were 1.12 (1.88) hours (95% CI = 0.71, 1.53).

3.6. Reduction in oral levodopa and levodopa-equivalent dose

At DBP baseline APO/APO patients were taking a mean (SD) oral levodopa dose of 951.9 (588.1) mg, while PBO/APO patients were taking 1003.4 (453.2) mg; mean (SD) oral levodopa at DBP baseline for these groups combined was 978.9 (519.2) mg.

In the OLP cohort reported here, there was a significantly greater reduction in oral levodopa dose at the end of the DBP (week 12) in APO-treated patients compared with placebo-treated patients (least squares mean [SE] −230.0 [54.1] mg and −83.1 [44.6] mg; p = 0.0369). By the end of the OLP, the mean (SD) reduction from DBP baseline in oral levodopa dose for all patients treated with APO in the OLP (n = 60) was −272.7 (515.0) mg.

At DBP baseline the two groups were well matched in terms of LED, with the APO-treated group taking a mean (SD) LED of 1502.7 (761.2)

mg and placebo-treated patients taking 1512.5 (593.4) mg. By the end of the OLP, the mean (SD) LED for all patients treated with APO in the OLP (n = 60) had reduced by −542.5 (674.2) mg.

3.7. Other efficacy parameters

Results for PGIC showed that at weeks 24, 36, 48, and 64 of the OLP, APO treatment was associated with improved scores. At the end of the OLP 75.0% of patients noted some improvement in their general health status as assessed by PGIC.

There were no substantial changes for either group at any time point from the DBP baseline to the end of the OLP in UPDRS Part III motor scores during ON or in PDQ-8 scores. An exploratory analysis of the combined scores for item 4.3 (time spent in OFF) and item 4.4 (functional impact of fluctuations) showed an improvement from a mean (SD) score of 4.7 (1.4) at DBP baseline reducing to 3.1 (1.6) at week 64.

4. Discussion

The TOLEDO study is the first double-blind, placebo-controlled, multicenter trial of apomorphine infusion in PD patients who experience persistent motor fluctuations and >3 h of OFF time per day despite optimized oral/transdermal medication. The results at the end of the OLP demonstrate that it is well-tolerated and remains effective, with sustained reduction in OFF time and increase in ON time without troublesome dyskinesia, when used for up to 64 weeks. These findings were reflected in the patients' own view of the overall treatment effect, as assessed by PGIC, with three-quarters of patients noting improvement in their health status at the end of the OLP.

The good tolerability of APO infusion over the duration of the OLP was as expected from observations in the DBP and extensive clinical experience. Treatment-emergent AEs were more common in APO-treated patients than in those who received placebo during the DBP, but the nature and frequency of AEs during both study phases was in accordance with the known safety profile of APO. Injection site reactions, somnolence and nausea, usually mild or moderate, were the most frequent treatment-related AEs throughout the study.

Results for the occurrence of infusion site nodules found in our study are consistent with experience in clinical practice with apomorphine infusion. These occur due to a local inflammatory reaction whose precise pathological mechanism remains unknown [19]. However, it is recognized that in order to minimize the development of skin nodules with apomorphine infusion treatment, there should be a focus on good skin management and that this is key to achieving good long-term outcomes. Training in skin management was given by the investigators to patients at the start of the trial. Where cases of skin nodules occurred, the main action taken by the investigator was reminding the patient of suitable skin management techniques and providing additional training as needed. This included skin hygiene, rotating the site of needle insertion, massage of infusion site, use of silicone patches, switching to Teflon needles, or ultrasound. Notably, approximately 75% of cases of skin nodules that occurred during the study were either resolved or resolving when the patient completed the trial. This finding highlights that skin nodules can often be managed effectively and do not necessarily require cessation of apomorphine infusion treatment, as is often assumed.

The observed changes in the ESS were only slightly above the normal range of 0–10 (mild excessive daytime sleepiness is defined as a score of 11–12) and only one patient discontinued treatment due to somnolence.

In this study, a history of impulse control disorders was not an exclusion criterion for participation. The tolerability of APO infusion was found to be good with respect to the occurrence of impulse control-related behavioral changes. The observed cases of impulse control disorders and punding were all mild in severity and some were reversible, with a relatively low incidence (less than 10% of patients). These findings are in keeping with other reports for APO infusion [20,21], suggesting better tolerability than reported for oral dopamine agonists [22,23], although the duration of the observation period and the lack of a direct comparison limit conclusions.

The overall incidence of AEs was found to decline with continued use, in keeping with clinical observations that, if new AEs occur, they tend to do so early after treatment initiation and less commonly once patients have achieved a stable APO infusion rate.

There was a single case of reversible autoimmune hemolytic anemia. This has been recorded as a rare complication with subcutaneous APO infusion [1,3], highlighting that, in clinical practice, patients and carers should be advised about possible symptoms and signs of anemia, and hematology tests should be performed when patients present with symptoms potentially due to anemia.

The results for patients who completed the DBP and continued into the 52-week OLP of the study confirmed that efficacy and tolerability were reproducible in patients who switched from placebo to APO. Those patients who continued on APO experienced some further improvements in OFF time and OWTD during the OLP.

Patients were able to substantially reduce their overall intake of concomitant anti-PD medication over the course of the study. In the OLP safety set reported here, those randomized to APO during the DBP had experienced significantly greater reductions in daily levodopa and LED between baseline and week 12 compared with the placebo group. For patients who continued on APO into the OLP, baseline oral levodopa and LED were reduced further by the end of the OLP, indicating that over time, despite stable APO flow rates, the need for additional anti-PD medication continues to decline. Overall, the long-term findings show that APO infusion therapy can relieve the overall burden of oral medication, which in advanced PD often means taking a large number of tablets at very specific times throughout the day.

No substantial changes were observed in PDQ-8 scores when comparing DBP baseline and week 64. The statistically significant difference seen between groups at week 6 was no longer detectable later on and scores remained stable. The lack of impact on quality of life as measured in TOLEDO contrasts with other studies of APO infusion, which have shown significant improvements [20,24–26].

At the end of the OLP, mean daily OFF time was reduced by 53% compared to DBP baseline but was not completely abolished, despite continuous administration of a dopaminergic drug by a route that makes it independent of the gastrointestinal tract. This is also seen with intestinal levodopa infusion [27]. Possible reasons include the possibility that some patients may not use a suprathreshold dose (for instance due to tolerability, or because flow rates are not pushed further by the physicians) [7]. None of the patients in TOLEDO used APO infusion for a full 24 h, which is a valuable option in clinical practice for patients with troublesome nocturnal OFFs [1,2]. A subcutaneous APO injection for early morning OFFs can reduce a delayed start up time in patients on waking day infusions, further reducing the overall daily OFF duration.

Worsening or treatment-emergent dyskinesias are a known limitation of some PD medications. A recent retrospective analysis of patients treated with intrajejunal levodopa/carbidopa gel infusion found an association with the development of complex or atypical biphasic dyskinesias in some patients [28]. In TOLEDO, the increase in OWTD seen with APO infusion at the end of the DBP was maintained at the end of the OLP with modest further improvements. While the observed reduction in troublesome dyskinesia during ON periods cannot be considered as proof of a direct, causative effect of APO infusion, it is encouraging to note that no patients in the TOLEDO study had to discontinue treatment due to dyskinesia. There was relatively little ON time with troublesome dyskinesia at baseline in patients who entered the OLP and minimal changes were observed throughout the study.

The TOLEDO study shows the safety, tolerability and long-term efficacy of individually-titrated doses of apomorphine infusion in PD patients who have persistent motor fluctuations that cannot be adequately controlled with optimized oral/transdermal medication. Apomorphine infusion therapy was found to allow substantial reductions in oral PD medication.

Compared to intrajejunal levodopa/carbidopa gel and deep brain stimulation, apomorphine infusion represents a minimally-invasive and easily reversible treatment option, which now has high level evidence for its efficacy and good safety profile and which should be considered in eligible patients once motor fluctuations begin to escape control.

Author contributions

RK: Designed the trial, contributed to data acquisition, interpreted data, wrote the report, and approved the final draft. **WP:** Designed the trial, contributed to data acquisition, interpreted data, contributed to writing the report, and approved the final draft. **OR:** Designed the trial, contributed to data acquisition, interpreted data, contributed to writing the report, and approved the final draft. **CT:** Designed the trial, contributed to data acquisition, interpreted data, contributed to writing the report, and approved the final draft. **GD:** Designed the trial, interpreted data, contributed to writing the report, and approved the final draft. **KRC:** Contributed to data acquisition, interpreted data, contributed to writing the report, and approved the final draft. **TH:** Contributed to data acquisition, interpreted data, contributed to writing the report, and approved the final draft. **TvL:** Contributed to data acquisition, interpreted data, contributed to writing the report, and approved the final draft. **DL:** Medical oversight, contributed to data acquisition, interpreted data, contributed to writing the report, and approved the final draft. **HS:** Employee of Sigma Statistical Services; contracted statistician to Britannia Pharmaceuticals Ltd. Interpreted results and approved the final draft. **AL:** Designed the trial, interpreted data, contributed to writing the report, and approved the final draft.

Data sharing statement

The TOLEDO study data will be available to investigators whose proposed use of the data has been approved by an independent review committee.

Individual participant data that underlie the results reported in this Article will be shared (text, tables, and figures), after de-identification, along with the study protocol, statistical analysis plan, and analytical code.

These data will be available 3 months after the Article's publication and will be available for 36 months from publication. Requests and proposals should be directed to CTD@britannia-pharm.co.uk.

To gain access, data requestors will need to sign a data access agreement.

Author disclosures

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