

Apomorphine Subcutaneous Infusion in Parkinson's Disease Patients With Persistent Motor Fluctuations: A Multicentre, Double-Blind, Randomised, Placebo-Controlled Study (TOLEDO Study)

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Contributors

The TOLEDO Steering Committee (RK, AL, WP, OR, CT and GD, plus representatives of the sponsor) developed the study.

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.

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HS: Employee of Sigma Statistical Services; contracted statistician to Britannia Pharmaceuticals Ltd. Performed statistical analysis, interpreted results and approved the final draft.

AL: Designed the trial, interpreted data, contributed to writing the report, and approved the final draft.

Conflicts of interest

RK has received fees for consulting or speaking, research grants or non-financial support from AbbVie, Acorda, Adamas, AOP Orphan, Bial, Biotie, Britannia, Cynapsus, Global Kinetics Corporation, Grünenthal, Licher, Novartis, Stada, UCB and Zambon.

WP has received consultancy and lecture fees related to PD drug development from AbbVie, AstraZeneca, Bial, Biogen, Cynapsus, Britannia, Grünenthal, Intec, Ipsen, Lundbeck, Merz Pharmaceuticals, Novartis, NeuroDerm, Orion Pharma, Prexton, Teva, UCB and Zambon.

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CT has received scientific grants from the Michael J. Fox Foundation, the European Commission Horizon 2020 Program: ‘Propag-Ageing’, MundiPharma, Vifor, acted as scientific advisor for Britannia, Novartis, UCB, MundiPharma, Vifor, Benevolent, Orion Pharma, Pfizer, and received speaker’s honoraria from Grünenthal, UCB and AbbVie.

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KS was an employee of Britannia Pharmaceuticals Ltd when the study was conducted.

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HS has received consultancy fees from Britannia.

AL has received consultancy fees from Britannia Pharmaceuticals and Bial Portela; honoraria from Profile Pharmaceuticals, Teva, Lundbeck, NordiciInfu Care, NeuroDerm, UCB and Roche.

Abstract

Background The aim of this randomised, placebo-controlled, double-blind, multicentre trial was to investigate the efficacy and safety of apomorphine infusion over placebo in patients with Parkinson's disease (PD) and persistent motor fluctuations despite optimised oral/transdermal treatment.

Methods Subjects were enrolled at 23 European centres and had a diagnosis of PD of >3 years' duration with motor fluctuations not adequately controlled on medical treatment. Subjects gave written informed consent; local ethics committees approved the study. Patients were randomised in a 1:1 ratio stratified by site to receive apomorphine or placebo saline infusion during waking hours (16±2 hours) at 3–8 mg/hour for 12 weeks. Based on individual efficacy and tolerability, the flow rate of the study drug and oral medication were adjusted

during 4 weeks, followed by an 8-week maintenance period. The primary endpoint was the absolute change in daily 'off' time based on patient diaries (intention-to-treat analysis).

Findings 107 patients were randomised and 106 included in the full-analysis set (one did not provide any post-baseline efficacy data). Apomorphine infusion (n=53; mean [\pm SD] final dose: 4.68 \pm 1.50 mg/hour) provided statistically significantly greater reduction in 'off' time compared with placebo (n=53); difference between treatment groups of -1.89 hours (95% CI: -3.16, -0.62; p=0.0025). Apomorphine was well tolerated without unexpected safety signals.

Interpretation The TOLEDO study provides the level-1 evidence previously lacking. Apomorphine infusion resulted in statistically significant and clinically meaningful 'off' time reduction without increasing dyskinesias in PD patients with persistent motor fluctuations despite optimised oral/transdermal therapy.

Funding

Britannia Pharmaceuticals Limited funded the study, registered at ClinicalTrials.gov (NCT02006121).

Keywords

Parkinson's disease; apomorphine subcutaneous infusion; motor fluctuations; off-time; dyskinesia.

Introduction

Parkinson's disease (PD) is characterised by neurodegeneration of the substantia nigra with progressive striatal dopamine deficiency and motor symptoms.¹

Dopamine replacement therapy is efficacious but in most patients levodopa eventually leads to motor fluctuations as the disease progresses. These are typically managed by redistributing levodopa and adding monoamine oxidase type B (MAO-B) inhibitors, catechol-O-methyl transferase (COMT) inhibitors, and oral/transdermal dopamine agonists.² Over time, motor fluctuations usually worsen, leading to significant periods of immobility and non-motor symptoms, and attempts to control fluctuations with oral medication may lead to disabling dyskinesia. Persistent motor complications may be managed by deep brain stimulation (DBS) or continuous dopaminergic drug delivery, using the subcutaneous infusion of the dopamine agonist apomorphine or the intestinal infusion of levodopa/carbidopa gel (LCIG). High-level evidence exists for the efficacy of DBS and LCIG, but both treatments are invasive and carry a specific spectrum of risks.³

Apomorphine is a potent dopamine receptor agonist with affinity for all dopamine receptor subtypes.⁴ It was first licensed in the United Kingdom (UK) in 1993 for PD based on an open-label, comparative study⁵ which demonstrated equivalent antiparkinsonian efficacy to levodopa, and it remains the only medication with the same symptomatic efficacy as levodopa. Subcutaneous apomorphine infusion is currently licensed for severe motor fluctuations and reimbursed by several healthcare systems across the world. Numerous short- and long-term uncontrolled studies have demonstrated its efficacy in reducing ‘off’ time (up to 80%), and most – but not all – also showed an improvement in dyskinesias and concomitant reductions in oral levodopa doses.^{4,6,7} Despite its long-standing clinical use, apomorphine infusion has never been tested in a randomised, controlled trial (RCT), which is a significant weakness in the formal evidence base for this therapeutic modality.

We present here results of the 12-week, double-blind phase of the TOLEDO study, the first prospective, randomised, placebo-controlled trial to investigate the efficacy and safety of apomorphine subcutaneous infusion in PD patients.

Methods

Study design

The TOLEDO study was a prospective, multicentre, Phase III study with the primary objective of demonstrating the efficacy of apomorphine subcutaneous infusion compared with placebo in levodopa-treated PD patients with persistent motor fluctuations despite optimised oral/transdermal medication. A secondary objective was to investigate the safety and tolerability of apomorphine infusion. The trial included a 12-week, parallel-group, double-blind, placebo-controlled phase (Figure 1) followed by a 52-week open-label phase. TOLEDO was performed in accordance with the International Conference of Harmonization guidelines on Good Clinical Practice E6 and the Declaration of Helsinki 2013.⁸ Prior to the start of the study, the study protocol, patient information sheet, and informed consent were approved by the independent ethics committees and the competent regulatory authorities in accordance with local legal requirements in each participating country.

Subjects

Participants were enrolled at 23 university and general hospitals specialised in the treatment of PD across Austria, Denmark, France, Germany, Spain, the Netherlands and the UK. Subjects were male or female patients aged ≥ 30 years with a diagnosis of PD of >3 years' duration, as defined by the Queen Square Brain Bank criteria (with the exception of affected relatives allowed),⁹ and levodopa-related motor fluctuations not adequately controlled on medical treatment, which had to include ≥ 4 daily intakes of oral levodopa and to be judged to

be optimal by the investigator. Patients' Hoehn & Yahr stage had to be ≤ 3 in the 'on' state and 2–5 in the 'off' state. They were required to have been on stable doses of oral medication for ≥ 4 weeks prior to enrolment, needed to be able to differentiate between their subjective 'on' and 'off' state and between 'on' with troublesome and non-troublesome dyskinesia and without dyskinesia, and to document those states in the diary. Eligible patients had to have an average of ≥ 3 hours of 'off' time per day for 2 days based on diaries at screening and baseline, with no day with < 2 hours 'off' time recorded.¹⁰ All oral or transdermal antiparkinsonian drugs available in the participating countries were permitted, except budipine.

Exclusion criteria included secondary and atypical parkinsonian syndromes, previous neurosurgical treatment for PD, previous use of apomorphine infusion, and treatment during the 28 days prior to enrolment with apomorphine injections, intrajejunal levodopa or any neuroleptic drug treatment. Patients were also excluded if they had severe freezing leading to falls during 'on', clinically relevant postural instability during 'on', or symptomatic, clinically relevant uncontrolled orthostatic hypotension, prolonged QT duration, clinically relevant cognitive decline (defined as Mini Mental State Examination score ≤ 24 or according to DSM IV-criteria) or psychosis judged to be at least moderate during the previous year or currently. Very mild visual hallucinations (illusions of passage or presence), with fully retained insight, were permitted. All patients provided written informed consent prior to enrolment.

Randomisation and masking

Eligible patients were randomised in a 1:1 ratio within a block size of 4 stratified by site to either apomorphine or placebo subcutaneous infusion, according to a central, computer-

generated randomisation code generated by the Biometric Department of Advanced Medical Services GmbH using SAS software. The Electronic Data Capture (EDC) system used for study was ClinCase, provided by Quadrantek Data Solutions Ltd. All study participants and investigators were masked to group assignment. Although success of masking was not formally assessed, every effort was made to maintain blinding throughout the study. There were two separate teams of investigators at each centre: Team 1 reviewed laboratory results, safety and tolerability, collected diary data and adjusted the dose of study drug and concomitant medication. Team 2 assessed Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) scores¹¹ and Patient Global Impression of Change (PGIC).¹² Neither team had access to data recorded or collected by the other team. Study participants and their carers were instructed not to discuss their medication or any observed effects or possible adverse events (AEs) with Team 2 investigators. All investigators were instructed not to communicate their own perception of possible treatment assignment to the other team of investigators, patients or carers.

Dosing

Apomorphine subcutaneous infusion was provided in 10 ml glass pre-filled syringes (manufactured by Catalent Pharma Solutions, Brussels, Belgium) and delivered as a 5 mg/ml solution for infusion using a Canè CRONO APO-Go infusion pump. A placebo saline infusion produced by the same manufacturer and identical to apomorphine in appearance, weight and packaging was provided in identical pre-filled syringes and administered using the same pump system.

The target dose of apomorphine was each patient's individual optimised dose at hourly flow rates of 3–8 mg, administered for approximately 16 hours of their waking day. Infusion times

of 14–18 hours were permissible and any shorter duration (minimum 12 hours) required an explanation by the investigator. Initiation of treatment was undertaken during a hospital stay of 5–10 days, where patients/carers received infusion-system training. Day-case hospitalisation was permitted in those centres where outpatient titration was already standard practice. Antiemetic pre-medication was administered according to local standards and the investigator's judgement. For domperidone, the recommended dose was 10 mg \leq 3 times/day starting three days before the infusion.¹³ On Day 1, patients received a starting dose of the study drug at a flow rate of 1 mg/hour. During the in-patient/day case dose-adjustment period, the flow rate could be adjusted daily by 0.5–1.0 mg/hour, and weekly after that up to the end of Week 4, until the maximum of 8 mg/hour or the highest tolerated dose was reached, whichever occurred first. Patients were required to be discharged on \geq 3 mg/hour.

Any reductions in concomitant PD medications were driven by the emergence of possible dopaminergic effects, in particular dyskinesias, nausea, orthostatic hypotension, or sleepiness. If applicable, oral medication was reduced in a hierarchical manner (Figure 1), with the aim of reducing and discontinuing oral/transdermal dopamine agonists first, followed by MAO-B inhibitors. For levodopa or combined levodopa/COMT, doses were to be reduced first, followed by an increase in the intervals between intakes. COMT inhibitors could be discontinued. Amantadine and anticholinergics were left unchanged. The titration period was followed by an 8-week maintenance period on stable doses. Use of the bolus function of the pump was not permitted and levodopa rescue doses for 'off' periods were limited to 300 mg/day during the titration phase and 200 mg/day during the maintenance phase. In addition, patients developing nocturnal 'off'-periods following discontinuation of controlled-release dopamine agonists could be re-started on that agonist up to the original dose at bed-time.

After completing the 12-week double-blind phase, or in the case of withdrawal due to lack of efficacy, patients were offered treatment with apomorphine infusion in the 52-week open-label phase of the trial.

Visits and evaluations

During the double-blind phase, visits were performed at baseline and at Weeks 2, 3, 4, 6, 8, 10, and 12. Patients received training in diary completion, including daily infusion time records. For two days prior to baseline, every day during the in-patient /day case stay, and for two days prior to each visit at Weeks 2, 3, 4, 6 and 12, patients completed the 24-hour home diary assessment of motor status at 30-minute intervals, recording periods when they were ‘on’ without dyskinesia, without troublesome dyskinesia or with troublesome dyskinesia, ‘off’ and sleeping. Additional evaluations at each visit included vital signs and safety assessments. Clinical laboratory variables were performed at baseline, at the end of the hospitalisation period, and then monthly.

Outcome measures and statistical analysis

The primary efficacy endpoint was the absolute change in time spent ‘off’ (derived from patient diaries) from baseline to the visit at Week 12. Secondary efficacy endpoints were response to therapy, defined as an ‘off’ time reduction of ≥ 2 hours from baseline, PGIC, absolute change in time spent ‘on’ without troublesome dyskinesia, change in oral levodopa dose and levodopa-equivalent dose (LED),¹⁴ change in MDS-UPDRS Part III (motor examination) scores during ‘on’ periods, and change in quality of life (QoL) assessed using the 8-item Parkinson’s Disease Questionnaire (PDQ-8).¹⁵ Safety assessments included evaluation of AEs and local tolerability, clinical and laboratory parameters, electrocardiograms, Questionnaire for Impulsive–Compulsive Disorders in PD (QUIP; long

version),¹⁶ Epworth Sleepiness Scale (ESS),¹⁷ and the Columbia Suicide Severity Rating Scale (C-SSRS).¹⁸

Sample size was calculated based on previous experience and a review of published data, and assumed an 'off' time baseline value of 6.5 hours would be reduced to 3.5 hours with apomorphine and to 5 hours with placebo.^{19,20} Thirty-four patients in each arm would provide 90% power with 5% two-sided significance to detect a treatment effect of 1.5 hours assuming a standard deviation (SD) of 1.75 and 2.5 hours 'off' time reduction for the apomorphine and placebo arms, respectively. Randomisation of 102 patients provided an additional 5% to allow for a non-parametric statistical test and an assumption that 30% would not be evaluable for the primary endpoint.

All randomised patients who received at least one dose of trial medication and for whom any post-baseline efficacy assessment was available were included in the analysis of baseline and efficacy data (full analysis set; FAS) using the intention-to-treat principle. Missing data for the primary endpoint were imputed using a last-observation-carried-forward (LOCF) approach. Sensitivity analyses were conducted using only post-titration values to perform LOCF, fitting a mixed model for repeated measurements (MMRM) assuming missing data were missing at random and multiple imputation (MI). Descriptive safety data is based on the safety dataset which comprised all patients who received at least one dose of trial medication and were analysed 'as treated'.

Apomorphine has been licensed and clinically used in all the study countries for many years. With the exception of mandated titration and prohibited use of bolus dosing, the trial design closely resembled routine clinical use. The study drug was identical to commercial product.

This low-risk study design negated the need for a Data Safety Board (DSB) but the trial was overseen by a steering committee of specialist PD neurologists with extensive apomorphine infusion experience. A planned blinded interim analysis confirmed the assumptions of sample size calculation but could not rule out potentially harmful worsening of symptoms in placebo treated patients due to increased ‘off’ time. The sponsor subsequently chartered Clintrex LLC (Independent Data Review Committee [IDRC]) who reviewed data for 76 randomised patients and found no undue risk and recommended continuation of the study as planned. Direct data transfer between the unblinded CRO staff and the IDRC meant no study staff were exposed to unblinded data.

Except for the model-based sensitivity analyses mentioned below, the Wilcoxon rank test was used to compare the treatment groups for continuous and ordinal variables. Fisher’s exact test was used to compare the treatment groups for nominal categorical variables. For the Model-based sensitivity analyses, MMRM used difference in least squares mean and MI used ANCOVA. The statistical package used was SAS 9.4.

Data sharing

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, figures, and appendices), after de-identification, along with the study protocol, statistical analysis plan and analytic code. These data will be available 3 months following 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.

Role of sponsor

The study was registered at ClinicalTrials.gov (NCT02006121). The trial protocol is available at: www.britannia-pharm.co.uk then click on the 'Research' tab. Britannia Pharmaceuticals Limited funded the study, participated in the study design, provided funding for editorial and formatting assistance (under corresponding author direction), and was responsible for data collection, monitoring and statistical analysis. Sponsor authors critically reviewed the manuscript and approved the final submission. All authors had full access to all data and were responsible for writing the manuscript. The corresponding author had the final responsibility for content and the decision to submit for publication.

Results

Between 3 March 2014 and 1 March 2016, 128 patients were screened for eligibility. One hundred and seven of them met the eligibility criteria, signed an approved informed consent, were enrolled and randomly assigned to a treatment group (apomorphine=53; placebo=54). One hundred and six patients met the protocol definition of 'evaluable' with a pre-and post-infusion efficacy assessments, so that their data contributed to efficacy analyses. One of these did not have any post-baseline diary data so did not contribute to the primary endpoint analysis using LOCF. Of those patients, 71 completed all 12 weeks of the study (apomorphine=41; placebo=30) (Figure 2) and a further 35 contributed off-time diary data to the primary endpoint.

Overall, 36 patients discontinued the double-blind phase before Week 12: 12 in the apomorphine group (2 switched early to the open-label phase, 10 discontinued the study) and 24 in the placebo group (16 switched early to the open-label phase, 8 discontinued the study).

The most common reasons for discontinuation were AEs in the apomorphine group (n=6; 11.3%) and lack of efficacy in the placebo group (n=16; 29.6%).

Baseline characteristics are summarised in Table 1; a breakdown of patients by country of origin is shown in Table S1 (Supplementary Material). Demographic variables were balanced across the treatment arms, as were anti-PD medications taken at baseline (Supplementary Material, Table S2).

The mean (\pm SD) final dose of study medication was 4.68 \pm 1.50 mg/hour (range: 1.5–8mg/hour) in the apomorphine arm and 5.76 \pm 1.79 mg/hour (range: 0–8.0 mg/hour) in the placebo arm.

Primary and secondary endpoints

Compared to subjects randomised to placebo infusions, patients on active apomorphine infusions had significantly greater reductions in their time spent ‘off’ as well as in time spent ‘on’ without troublesome dyskinesia (Table 2, Figure 3a). Significant differences in favour of apomorphine were also observed for a percentage of patients with ≥ 2 hours of ‘off’ time reduction, PGIC, and reduction in oral LED. The mean (\pm SD) change from baseline in ‘off’ time at week 12 was -2.47 (3.70) hours and -0.58 (2.80) hours for the apomorphine and placebo groups respectively. The difference in the changes in ‘off’ time between the groups from baseline to Week 12 was -1.89 hours (95% CI: -3.16, -0.62; p=0.0025). These results were consistent across pre-specified subgroups (gender and age group <65 years and ≥ 65 years; Supplementary Material, Figure S1) and the sensitivity analyses (Supplementary Material, Figure S2).

A significant positive improvement in ‘off’ time with apomorphine infusion was observed at Week 1 (treatment difference 1.62 hours) and was sustained over 12 weeks (Figure 3b). For absolute change in time spent ‘on’ without troublesome dyskinesia at Week 12, the difference between treatment groups was 1.97 hours (95% CI: 0.69, 3.24; $p=0.0008$) (Table 2). The proportion of patients who achieved ≥ 2 hours of ‘off’ time reduction at Week 12 was significantly higher for apomorphine than placebo (62.3% vs 28.8%; $p=0.0008$).

Post hoc analysis of absolute change in time spent ‘on’ with no dyskinesia, with non-troublesome dyskinesia and with troublesome dyskinesia are shown in Table S3 (Supplementary Material). Frequency of patients experiencing ‘on’ time with troublesome dyskinesia at baseline is shown in Table S4 (Supplementary Material).

The beneficial effects of apomorphine infusion were reflected in the improved PGIC scores ($p<0.0001$; Figure 4). At Week 12, 70.9% of patients in the apomorphine group stated improvement in their general health state compared with 17.6% in the placebo group (Table 2).

At Week 12, the mean change in oral levodopa dose from baseline showed a trend towards a greater reduction in the apomorphine infusion arm, but the difference between treatment groups did not reach statistical significance at the 5% level ($p=0.0615$; Table 2). There was a significantly greater reduction in oral LED between baseline and Week 12 in the apomorphine group compared with the placebo group (treatment difference [95% CI]: -328.5 mg [-535.2, -121.7]; $p=0.0014$; Figure 5 and Table 2). This difference between treatment groups was significant at all visits from Week 4. Mean LED at baseline and Week 12 by drug category is shown in Table S5 (Supplementary Material).

No significant difference at the two-sided 5% level between treatment groups was observed at Week 12 in QoL assessed using PDQ-8 or in measures of MDS-UPDRS Part III motor scores during 'on' periods (Table 2).

A list of exploratory efficacy and safety endpoints is shown in Table S6 (Supplementary Material).

Safety and tolerability

Overall, apomorphine infusion was well tolerated and the frequency and profile of treatment-related AEs were as predicted from its long-standing clinical use (Table 3); no unexpected safety signals were observed. Most events were mild or moderate in intensity and no deaths occurred during the study. The overall incidence of AEs was higher in the apomorphine group (92.6%) than in the placebo group (56.6%). The most common AEs were skin reactions, nausea and somnolence. A greater proportion of patients in the apomorphine group (48.1%) experienced AEs that required dose modification compared with the placebo group (11.3%). A summary of AEs at Week 12 for the safety set showing Clopper–Pearson exact confidence intervals is given in Table S7 (Supplementary Material).

AEs led to study withdrawal in six patients, all randomised to apomorphine. Three patients withdrew due to serious AEs (SAEs) (one severe hypotension, one myocardial infarction [MI], 1 persistent moderate abnormal haematology test [mild leukopenia and moderate anaemia with a lowest haemoglobin level of 9.5 mg, found not to be haemolytic]) and three further patients withdrew due to AEs (one visual hallucination, one moderate gait disturbance, one mild infusion site erythema, all of which resolved following cessation of the

study drug). Except for the MI, all AEs leading to withdrawal were considered at least possibly treatment related. No patients from the placebo group withdrew due to AEs.

SAEs occurred in five patients in the apomorphine group: In addition to the three cases that led to withdrawal, as described above, one case of severe intermittent confusion (resolved on dose reduction) and one severe infusion site cellulitis (resolved). In the placebo arm, two SAEs occurred: one severe depression, one colitis.

Neuropsychiatric changes observed in the apomorphine group were one case of mild hypersexuality (resolved on study drug dose reduction), two cases of mild punding (one resolved and the other did not; in each case the apomorphine dose was not changed), three episodes of confusion in a single patient (two mild and one severe, as listed above; all resolved on dose reduction), one case of moderate psychosis (resolved without dose change) and two cases of hallucinations (one mild which resolved without dose change; one moderate which resolved following cessation of the study drug, as listed above). In the placebo group there were three reported episodes of mild confusion (two patients) and two cases of mild hallucinations (all resolved).

No treatment group differences were observed in ESS scores, which were within the normal range for daytime sleepiness, or in C-SSRS scores.

Discussion

This is the first prospective, double-blind, randomised, placebo-controlled, multicentre study of apomorphine subcutaneous infusion in patients with PD and demonstrates that, in comparison with placebo, apomorphine subcutaneous infusion provided a significant

reduction in ‘off’ time in patients who were experiencing motor fluctuations that were persistent despite adjustments in their oral/transdermal medication. Importantly, this improvement was not achieved at the expense of worsening dyskinesias.

The treatment effect, or mean difference in ‘off’ time between the apomorphine and placebo groups, was almost two hours, both for the reduction in ‘off’ time and the increase in ‘on’ time without troublesome dyskinesia. While this effect size is smaller than previously reported for uncontrolled studies,^{4,6,7} inclusion of the placebo response brings the data in line with the total reduction in ‘off’ time as reported in open-label studies, and the majority (68%) of apomorphine-treated patients achieved more than two hours reduction in ‘off’ time. This magnitude of effect exceeds that seen with oral or transdermal medication when tested in placebo-controlled, randomised trials,²¹ and is around double the change in ‘off’ time identified as clinically meaningful to patients.²²

The clinical relevance of these results was highlighted by the PGIC, where significantly more patients in the apomorphine group rated themselves as improved than in the placebo group. Apomorphine infusion also allowed for a significant reduction in oral medication, which is considered to be the main reason why continuous dopaminergic drug delivery can reduce ‘off’ time without worsening dyskinesias. This reduction is likely of clinical importance to patients with motor complications as it may alleviate the burden of complex oral treatment regimens.

Although no precise definition was used for ‘treatment optimisation’ in terms of drug classes or sequence of therapy, enrolled patients were required to be receiving oral medication considered to be optimal by the investigator. All centres had long-standing experience in the

management of complex PD motor complications, including the indication for device-aided treatments for persistent motor fluctuations which, by definition, requires all other options to have been offered to the patients with insufficient benefit. Patients' baseline characteristics, including antiparkinsonian medication, were similar to those reported in other studies of treatments for persistent motor complications.^{2,23} In contrast to the TOLEDO study, the design of the LCIG study involved discontinuation of COMT inhibitors and slow release levodopa preparations before randomisation (for conversion into immediate-release and intestinal levodopa) and it allowed treatment optimisation in all participants (due to the double-dummy design), resulting in greater levodopa doses at final visit compared to baseline in both arms.

The lack of a significant effect on MDS-UPDRS Part III motor scores during 'on' periods was expected and also supports the fact that eligible patients were receiving optimised oral or transdermal treatment at experienced centres.

AE reports and tolerability were in line with those reported in previous observational studies,^{4,6} with most apomorphine-treated patients experiencing at least one AE during the study. All six AEs that led to discontinuation occurred in the apomorphine arm and five were classified as at least possibly related to treatment. However, none had a sustained negative effect, and all were reversed on cessation of treatment. The only reported case of infusion site reaction classified as severe resolved without leading to withdrawal. Somnolence was not uncommon with apomorphine but was severe in only one patient, despite the concomitant use of oral dopamine agonist treatment by around half of the patients randomised to apomorphine. Neuropsychiatric AEs occurred more commonly in the apomorphine arm, but

almost all resolved; the only case of impulse control disorder was a mild and short-lasting case of hypersexuality which resolved on dose reduction.

From a practical viewpoint, our study shows that some patients tolerate and receive benefit from doses exceeding the common range of hourly flow rates currently used. Many centres use higher flow rates than the mean dose in our study and it is possible that the full potential of apomorphine has not been exploited here. It is also noteworthy that while most patients were initiated as inpatients, outpatient initiation was also possible.

TOLEDO was not powered to study an antidyskinetic effect of apomorphine infusion, which had been observed in many open-label studies. 'On' time without troublesome dyskinesia increased significantly but, as in the randomised LCIG study,²³ baseline dyskinesia severity was relatively low, which may explain the lack of a significant change in existing dyskinesias. Dyskinesias were reported as an AE in 14.8% of apomorphine-treated patients; however, the majority of these instances (five out of eight patients) were limited to the dose-adjustment phase where dyskinesias were used as a trigger for oral dose reduction.

The TOLEDO study is an important addition to the evidence-base for apomorphine infusion in PD. However, our study had some limitations.

Almost one-third of patients did not complete the full 12-week, double-blind phase. Half of these (18 of 36 patients) switched into the open-label phase early. In nearly all cases (17 of 18) this was due to lack of study drug efficacy, and 16 of these 18 patients were from the placebo arm. The rate of patients choosing this option had been expected to be higher in the placebo arm, and this can be considered an indirect indicator of superior efficacy of

apomorphine. Nevertheless, the uneven rates of discontinuation may have caused a degree of bias. In addition, in clinical practice, oral dopamine agonists are often either discontinued before starting apomorphine, or gradually reduced and discontinued after starting treatment, usually more rapidly than in our study. Here, oral dopamine agonists were reduced slowly or in some cases not discontinued completely. Thus, dual agonist treatment may have contributed to AEs. Offering patients the option of switching to open-label apomorphine infusion was considered necessary for ethical reasons because the study was performed in countries where apomorphine is part of standard clinical management.

Although blinding success was not formally assessed, considerable efforts were made to maintain blinding throughout the study. However, some inherent features and practical aspects of apomorphine infusion therapy (including its rapid and powerful onset of effect,² the common requirement to reduce oral medication, and relatively frequent visible changes at the needle insertion site) could potentially have influenced blinding. Although patients were required to be apomorphine infusion naïve, use of apomorphine injections in the past was allowed, to reflect the population who would normally be offered apomorphine infusion. While the onset of clinical effect of the infusion is slower than with injections, and although the dose was increased gradually, it is conceivable that familiarity with the drug's effects may have occurred. In addition, the MDS-UPDRS was the only outcome measure that was directly clinician-assessed and a similar familiarity with the effects of apomorphine may have had an impact on blinding

The relatively short study duration may have precluded opportunities for some important clinical benefits. In clinical practice the process of adjusting the flow rate of apomorphine and oral medication sometimes exceeds 4 weeks. For example, clinicians aim at greater oral

dose reductions when dyskinesias are a concern, and maximum dyskinesia reduction may take up to several months.²⁴ The relatively short dose-adjustment period and overall study duration, as well as the insufficient power of the study, may also explain why a significant effect on patient quality of life was not demonstrated in this study, despite the significant benefit of apomorphine on PGIC. Such an effect has otherwise been quite consistently shown in open-label studies of apomorphine infusion, including in longer-term and multi-centre studies.²⁵⁻²⁷ Shorter-term (12–18-weeks) randomised trials of other efficacious antiparkinsonian medications have also failed to detect changes on QoL scales.^{28,29} The results of the 52-week open-label phase will show whether patients randomised to active drug went on to improve further once the doses of apomorphine and oral drugs could be adjusted individually.

In summary, the TOLEDO study is the first randomised, double-blind, adequately powered and well-controlled study in patients with PD to confirm the beneficial clinical effects of apomorphine infusion, reported in uncontrolled studies over many years, on motor fluctuations that persist despite adjustments in oral/transdermal medication. Continuous subcutaneous administration of apomorphine allows the dosage and number of administrations of shorter-acting oral PD medication to be reduced. Although no comparative, randomised studies versus LCIG exist, both infusion treatments have similar effect sizes²⁸ and apomorphine infusion is easily reversible and less invasive than LCIG, which requires the insertion of a gastric tube.

Our study aimed to reflect actual clinical practice, including regional differences, and to fairly represent the population of PD patients who are routinely offered this treatment. The results provide high-level evidence that apomorphine infusion leads to a pronounced

improvement in ‘off’ time, which is associated with an increase in good ‘on’ time and is clinically meaningful in the patients’ own view.

The results of the TOLEDO study reflect the positive ‘real world’ effects observed by clinicians over many years and support the findings of previous open-label studies. In addition to the confirmatory evidence that this RCT now provides for the development of PD treatment guidelines, it is hoped that it will also provide practical guidance for clinicians so that apomorphine infusion can be offered and reimbursed more widely as an effective treatment option.

Research in context

Evidence before this study

The long-term management of Parkinson’s disease (PD) is very commonly limited by the development of motor complications. In some patients, motor fluctuations are persistent despite repeated adjustments of oral (and transdermal) medication, including the use of long-acting formulations. The dopamine agonist apomorphine, which acts on all dopamine receptor subtypes and is administered subcutaneously, has been licensed since 1993 as a treatment option for the management of motor fluctuations in patients with PD which cannot be sufficiently controlled by oral PD medication. Since that time, it has been used in clinical practice in many countries. The efficacy of intermittent apomorphine injection therapy has been demonstrated in randomised studies. In contrast, the positive clinical experience with apomorphine infusion has been supported by many uncontrolled, open-label studies, but a search of PubMed up to February 2014 using the search terms ‘apomorphine’ and ‘infusion’ was not able to identify any randomised, double-blind, placebo-controlled clinical trials

assessing the efficacy and safety of apomorphine delivered as a continuous infusion in patients with PD experiencing persistent motor fluctuations after adjustments in oral/transdermal medication.

Added value of this study

The TOLEDO Study is the first randomised, double-blind clinical trial to investigate the efficacy, safety and tolerability of apomorphine subcutaneous infusion compared with placebo in PD patients whose motor fluctuations are uncontrolled despite optimised oral PD therapy. It will therefore provide the high-level evidence currently lacking.

Implications of all the available evidence

The results of the double-blind phase of the TOLEDO Study provide the first confirmation from a large, randomised clinical trial that apomorphine infusion can provide a significant and clinically meaningful reduction in ‘off’ time without increasing dyskinesias and is an effective treatment strategy for PD patients whose motor fluctuations remain uncontrolled despite optimised oral/transdermal therapy. The treatment effect was found to be of the same magnitude as that observed in the only other large, randomised study of an infusion therapy in PD patients, of intestinal levodopa/carbidopa gel infusion, and exceeds that seen with oral or transdermal medication when tested in the setting a placebo-controlled, randomised trial. Continuous infusion of apomorphine was well-tolerated in this population, which included older PD patients, and also allowed for a significant reduction in the required doses of concomitant oral PD medications. Apomorphine infusion has been in widespread clinical use for the treatment of motor fluctuations in PD patients in many countries for several decades, despite the lack of confirmatory evidence from an RCT. The TOLEDO study now provides this evidence and can help inform the development of PD treatment guidelines. Importantly, it provides clinicians with guidance on the practical use of apomorphine infusion for the

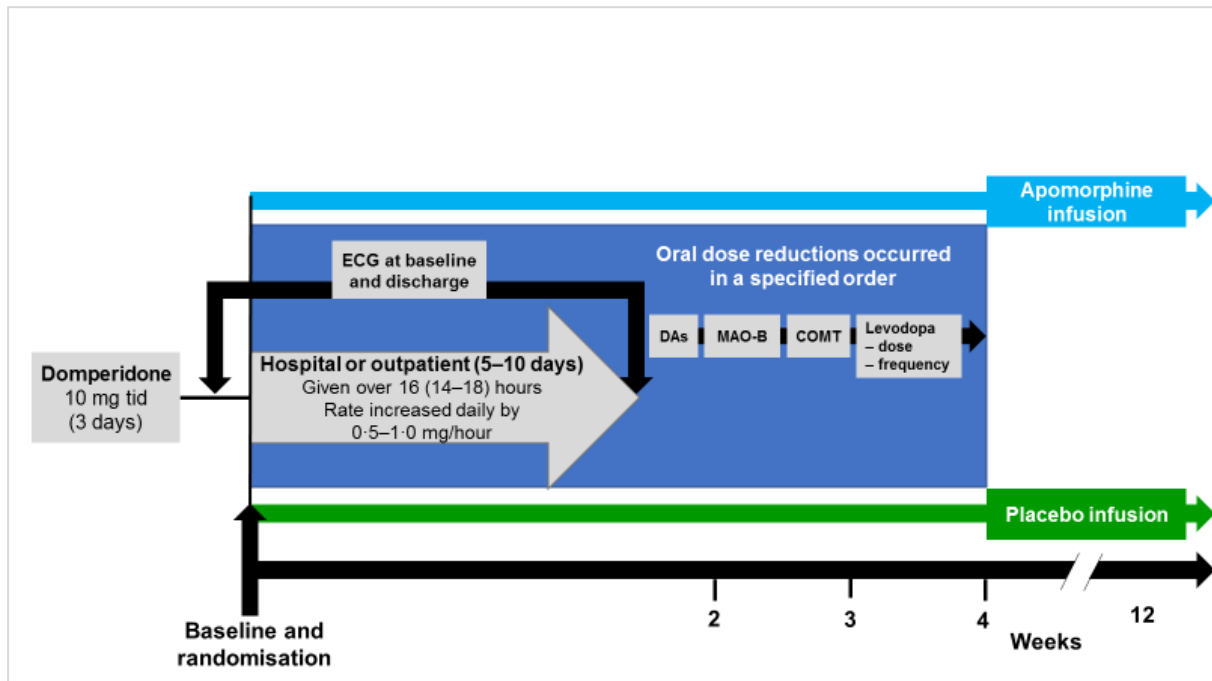
effective management of suitable PD patients in routine clinical practice, which should encourage its wider use and reimbursement.

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Figures and Tables

Figure 1. TOLEDO study design – 12-week double-blind phase.



COMT, catechol-O-methyl transferase inhibitor; DA, dopamine agonist; ECG electrocardiogram; MAO-B, monoamine oxidase-B inhibitor; tid, three times daily. Following completion of a 12-week, parallel group, double-blind, placebo-controlled phase, or in case of withdrawal due to lack of efficacy, patients could enter a 52-week open-label phase.

Figure 2. CONSORT diagram.

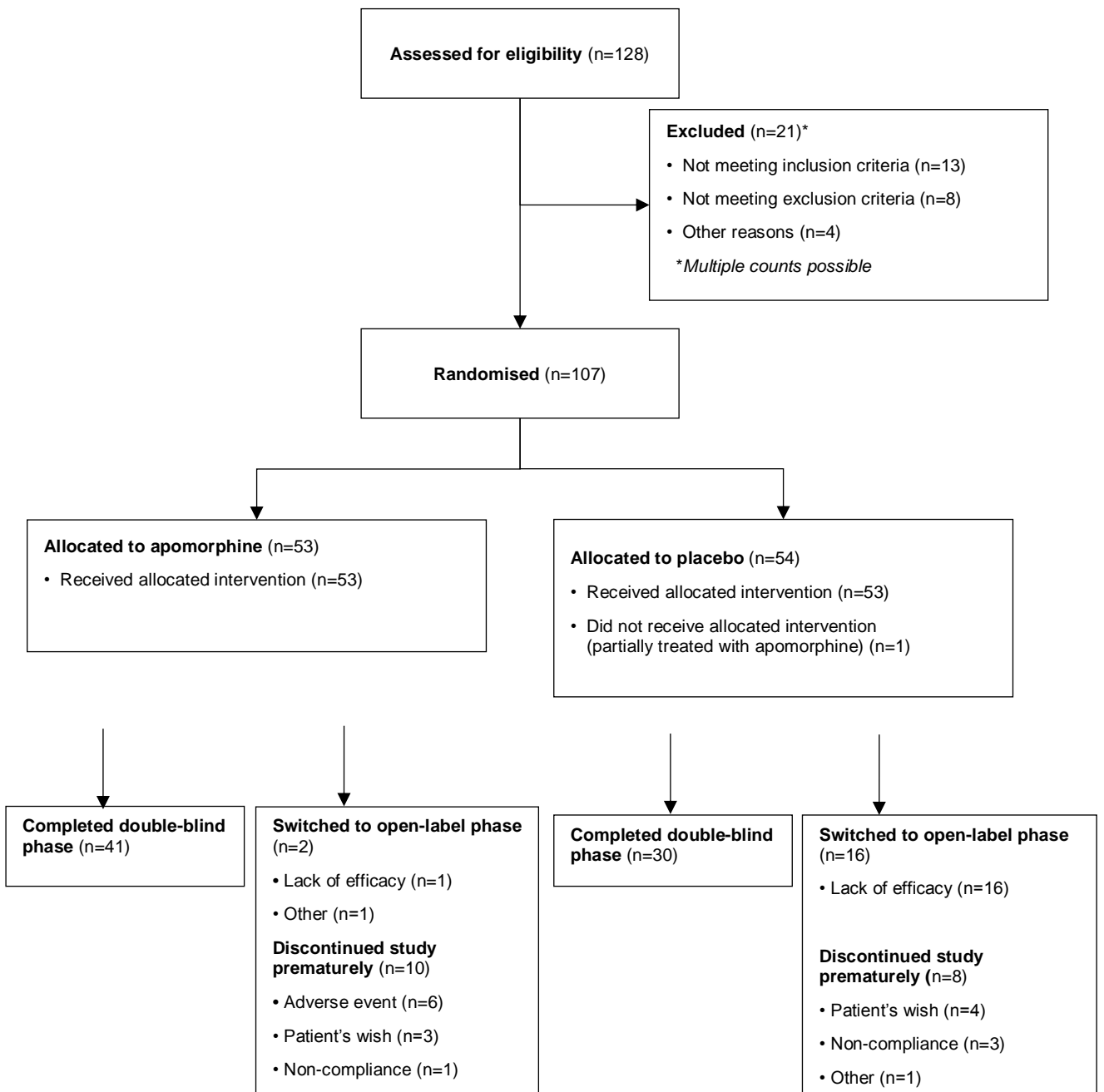


Figure 3a. Change in the various PD motor states between baseline and Week 12 based on home diary results.

Values are 95% confidence interval for the mean. LOCF, last observation carried forward. P-value is apomorphine versus placebo using Wilcoxon rank test.

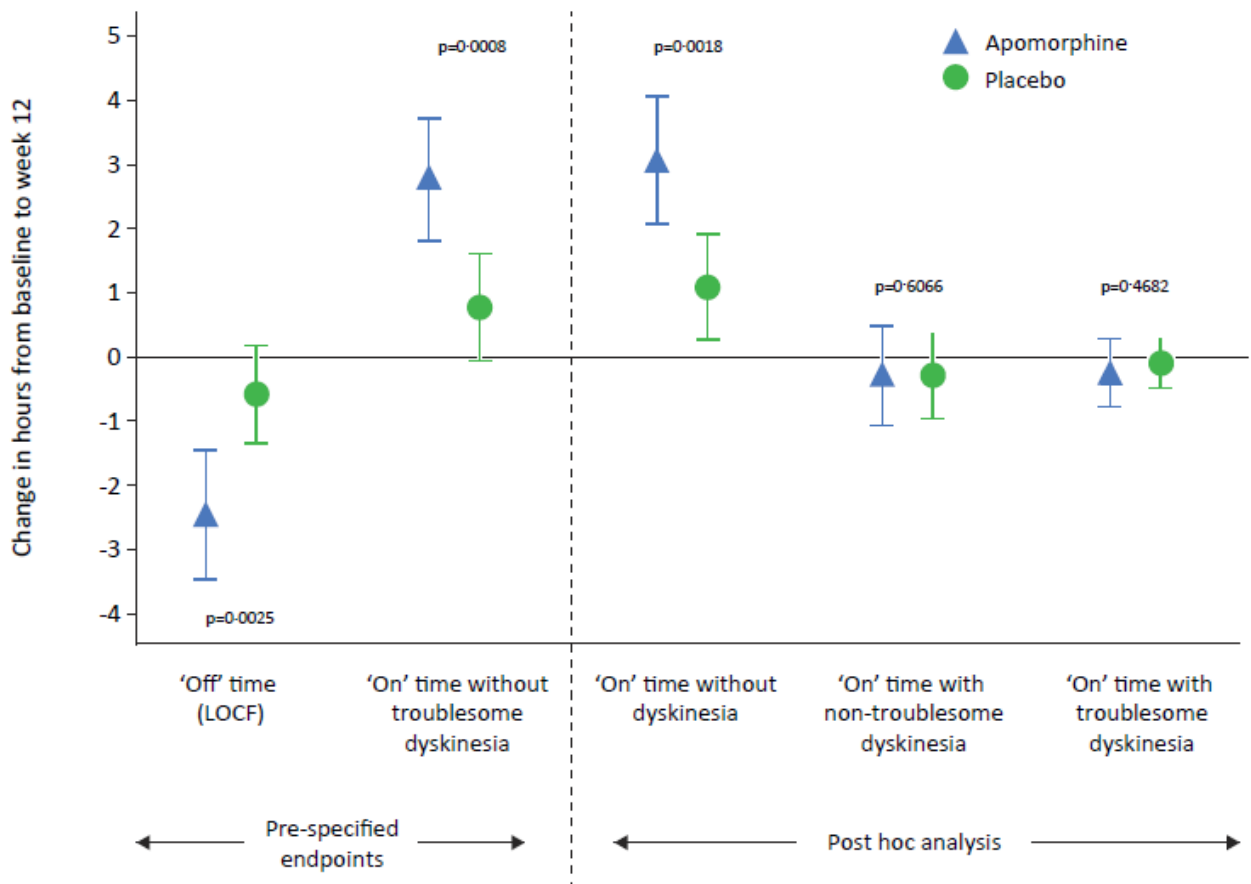


Figure 3b. PD motor states at each visit based on home diary results.

For each variable, data shown are the average from the motor symptom diary for the 2 consecutive days prior to the visit. Values are 95% confidence interval for the mean. LOCF, last observation carried forward. P-value is apomorphine versus placebo using Wilcoxon rank test.

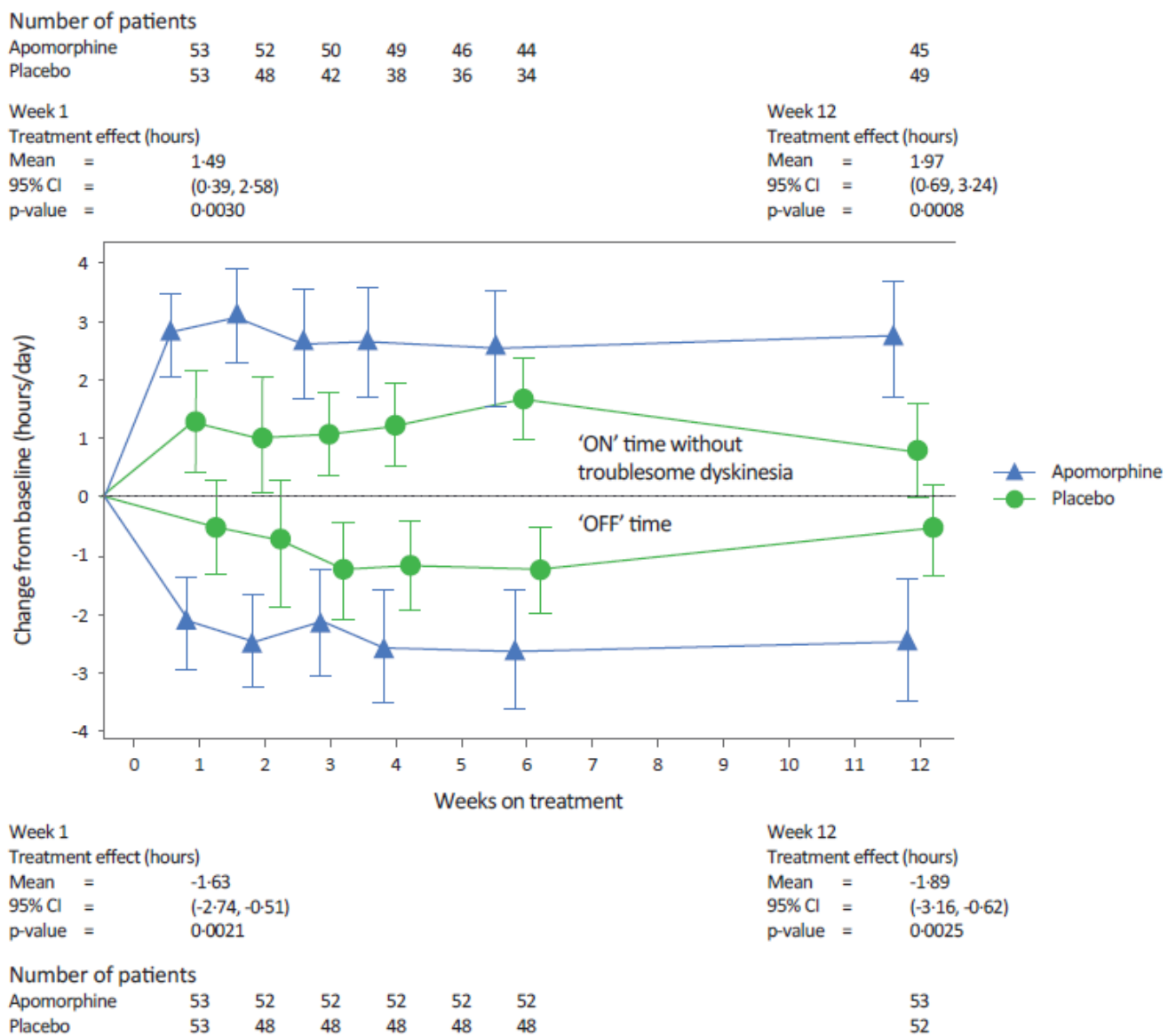


Figure 4. Patient Global Impression of Change from baseline to Week 12.

P-value is apomorphine versus placebo using Wilcoxon rank test.

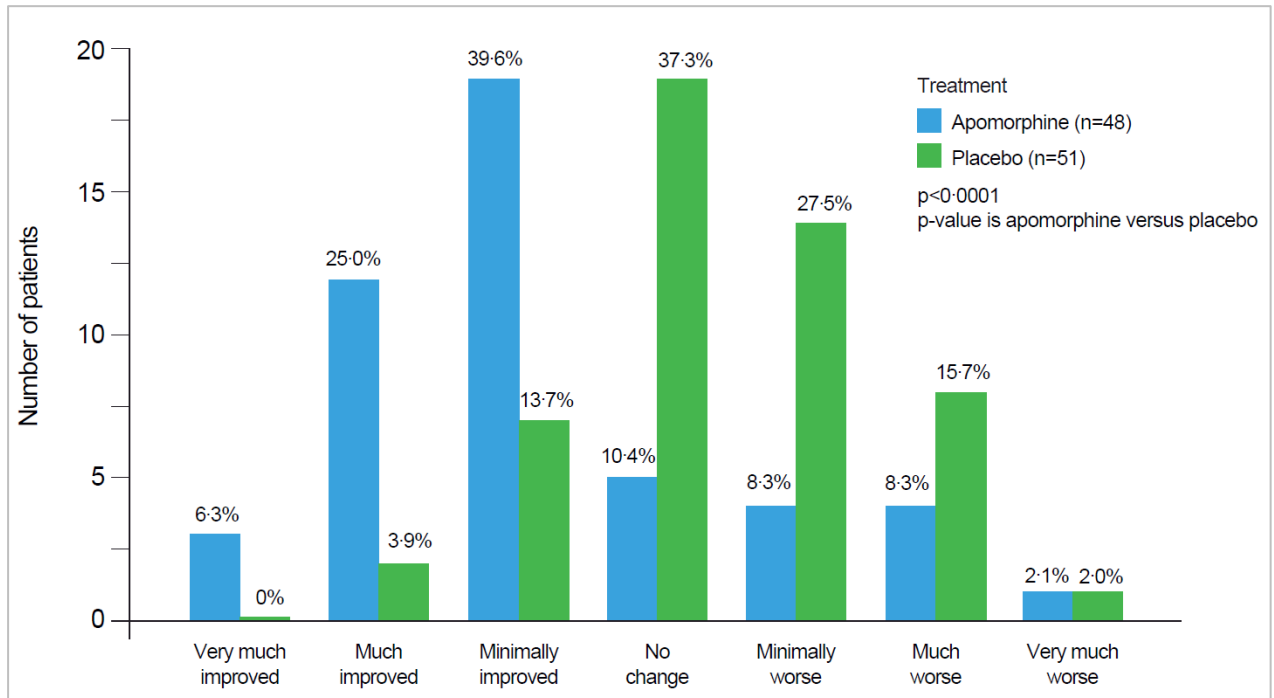
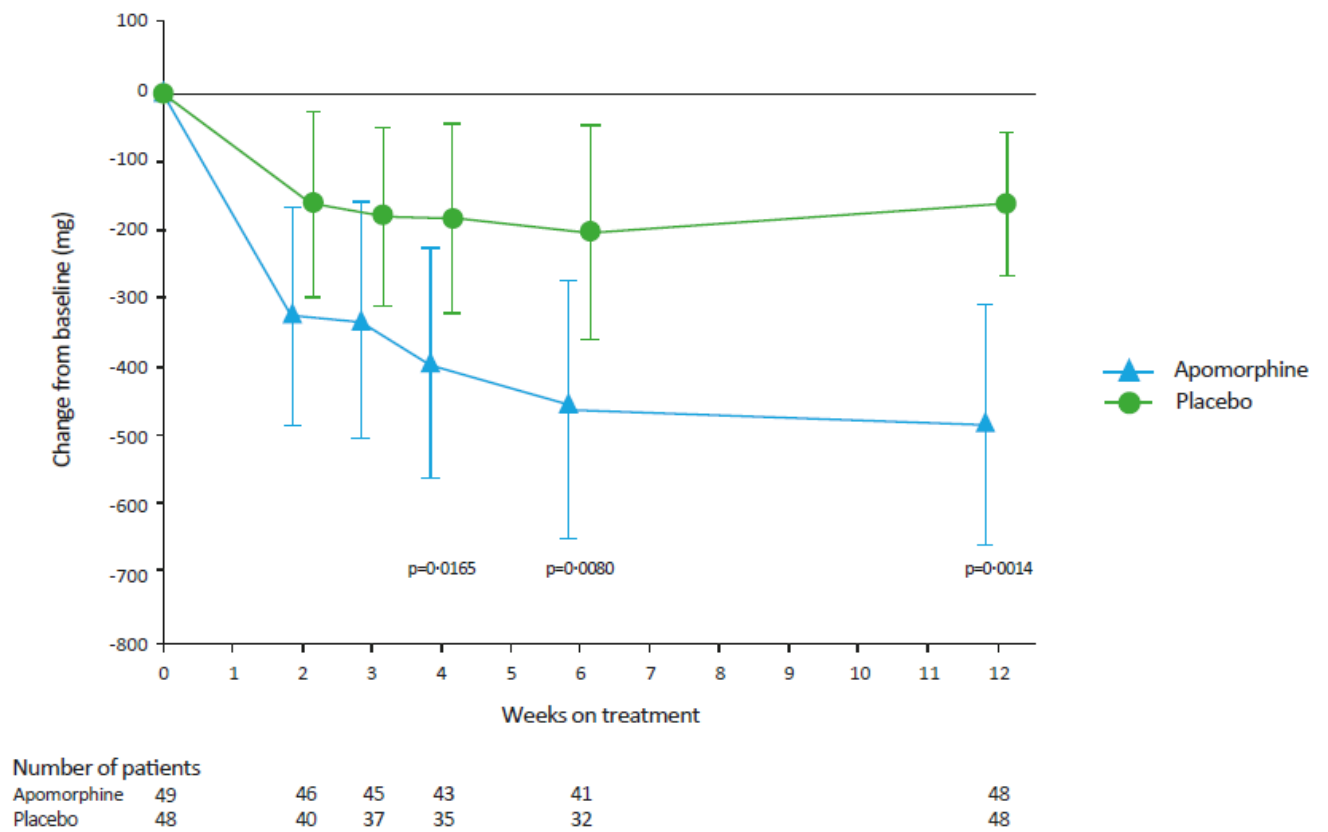


Figure 5. Change in levodopa-equivalent dose (mg) from baseline to Week 12 (full analysis set*).

Values are 95% confidence interval for the mean. P-value is apomorphine versus placebo using Wilcoxon rank test.



*Analysis excludes PRN use and missing data from three sites.

Table 1. Baseline characteristics (full analysis set).

	Apomorphine (n=53)	Placebo (n=53)	Total (n=106)
Gender			
Male, n (%)	34 (64.2%)	32 (60.4%)	66 (62.3%)
Female, n (%)	19 (35.8%)	21 (39.6%)	40 (37.7%)
Age, mean (SD)	63.6 (9.3)	63.0 (8.3)	63.3 (8.8)
Age group, n (%)			
<65 years	26 (49.1)	29 (54.7%)	55 (51.9%)
≥65 years	27 (50.9)	24 (45.3%)	51 (48.1%)
Duration of PD, years	11.8 (5.6)	10.6 (4.3)	11.2 (5.0)
Daily levodopa dose, mg (mean, SD)	920.4 (518.7)	989.0 (461.4)	954.38 (489.8)
Daily levodopa-equivalent dose, mg (mean, SD)	1,485.5 (702.6)	1,472.6 (567.9)	1,479.10 (636.2)
‘Off’ time, mean h/day (SD)	6.69 (2.23)	6.76 (2.51)	6.73 (2.36)
‘On’ time without troublesome dyskinesia, mean h/day (SD)	8.52 (2.36)	8.56 (2.39)	8.54 (2.36)
MDS-UPDRS Part III during ‘on’			
Mean (SD)	30.6 (13.65)	28.02 (15.25)	29.34 (14.43)
PDQ-8 score, mean (SD)	32.67 (15.03)	31.01 (12.66)	31.84 (13.86)

Table 2. Summary of efficacy findings at Week 12 (full analysis set).

Change from baseline to Week 12	Apomorphine (n=53)	Placebo (n=53)	Treatment difference (95% CI)	p-value
Primary endpoint				
Absolute change in time spent 'Off' (h/day)	-2.47	-0.58	-1.89 (-3.16, -0.62)	0.0025
Pre-specified secondary endpoints				
Number (%) of patients with response to therapy ('off' time reduction of ≥ 2 hours)	33 (62.3%)	15 (28.8%)	33.4% (15.48, 51.36)	0.0008
Patient Global Impression of Change (mean score at Week 12)	3.2	4.4	-1.20 (-1.71, -0.69)	<0.0001
Absolute change in time spent 'On' without troublesome dyskinesia (h/day)	2.77	0.8	1.97 (0.69, 3.24)	0.0008
Change in oral levodopa dose, mg (mean, SD)	-207.8 (439.5)	-94.3 (273.4)	-113.5 (-262.3, 35.2)	0.0615
Change in levodopa-equivalent dose, mg (mean, SD)	-492.1 (618.3)	-163.7 (367.5)	-328.5 (-535.2, -121.7)	0.0014
Change in MDS-UPDRS Part III motor scores during 'on' periods	-3.42	-0.89	-2.52 (-7.53, 2.48)	0.4642
Change in quality of life (PDQ-8)	-0.06	2.40	-2.47 (-7.62, 2.69)	0.3971

Table 3. Summary of adverse events (AE) by Week 12 (safety set).

Values are n (%)	Apomorphine (n=54)	Placebo (n=53)
At least one treatment-emergent AE (TEAE)	50 (92.6%)	30 (56.6%)
Most common TEAE (≥10% of patients)		
Skin nodules at infusion site	24 (44.4%)	0
Mild	20 (37.0%)	0
Moderate	4 (7.4%)	0
Nausea	12 (22.2%)	5 (9.4%)
Mild	10 (18.5%)	3 (5.7%)
Moderate	2 (3.7%)	2 (3.8%)
Somnolence	12 (22.2%)	2 (3.8%)
Mild	5 (9.3%)	1 (1.9%)
Moderate	6 (11.1%)	1 (1.9%)
Severe	1 (1.9%)	0
Infusion site erythema	9 (16.7%)	2 (3.8%)
Mild	8 (14.8%)	2 (3.8%)
Moderate	1 (1.9%)	0
Dyskinesia	8 (14.8%)	0
Mild	5 (9.3%)	0
Moderate	3 (5.6%)	0
Headache	7 (13.0%)	2 (3.8%)
Mild	6 (11.1%)	2 (3.8%)
Moderate	1 (1.9%)	0
Insomnia	6 (11.1%)	1 (1.9%)
Mild	2 (3.7%)	0
Moderate	4 (7.4%)	1 (1.9%)
At least one AE with a local intolerability (skin changes at injection site)	32 (59.3%)	8 (15.1%)
Severe AES	8 (14.8%)	2 (3.8%)
Serious AEs	5 (9.3%)	2 (3.8%)
AEs leading to study discontinuation	6 (11.1%)	0
AEs leading to dose modification	26 (48.1%)	6 (11.3%)

Supplementary material

Figure S1. Subgroup analysis: change from baseline in absolute time spent 'off' by gender and age group.

Values are mean (95% confidence intervals [CI]). FAS, full analysis set; last observation carried forward). P-value for the primary analysis is apomorphine versus placebo using Wilcoxon rank test. P-values for subgroups are for the interaction term between the subgroup and treatment.

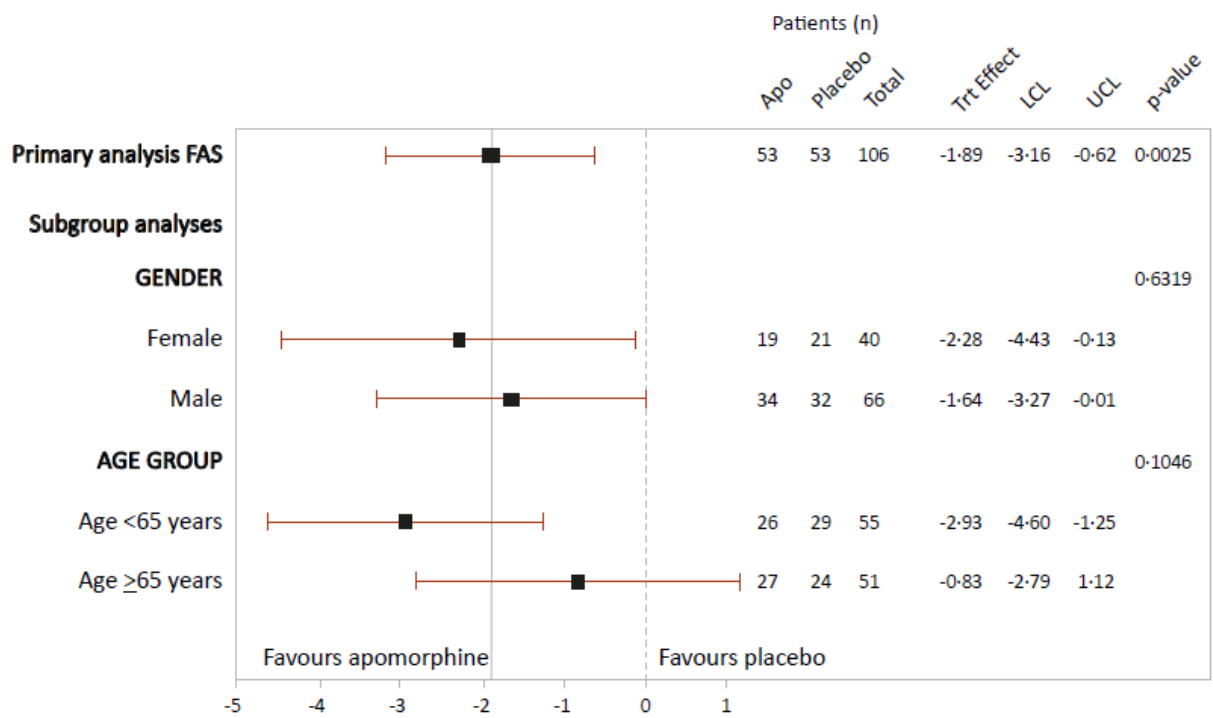
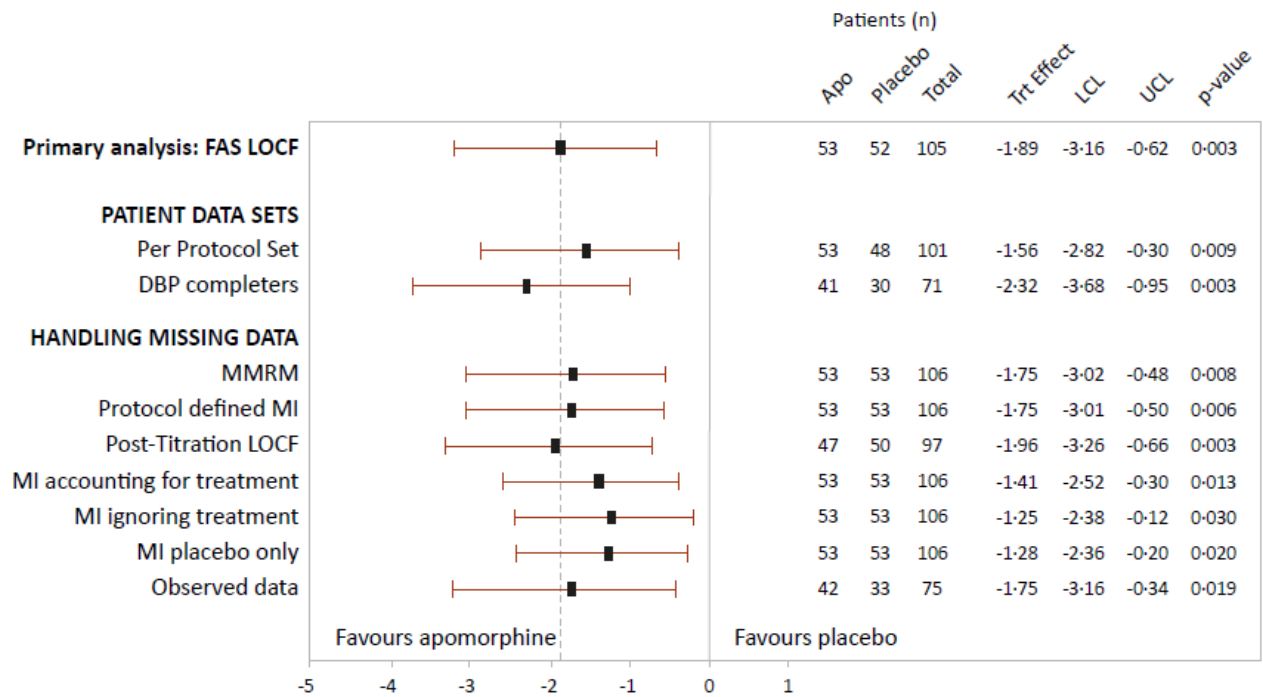


Figure S2. Sensitivity analysis Forest plot for change in ‘off’ time at Week 12.

Values are mean (95% confidence intervals [CI]). FAS, full analysis set; LOCF, last observation carried forward; LCL, lower confidence limit; UCL, upper confidence limit; MMRM, mixed models for repeated measure; MI, multiple imputation.



MMRM

Model includes treatment, visit, treatment*visit interaction and baseline ‘off’ time

Protocol defined MI

Multiple imputation (MI) of missing ‘off’ times using treatment and baseline ‘off’ time using Monte-Carlo Markov-Chain method with non-informative prior distribution

Post-titration LOCF

Last observation carried forward (LOCF) using only post-titration visits

MI accounting for treatment

MI of ‘off’ time change from baseline assuming monotone missing data using regression model containing treatment, baseline ‘off’ time and observed/imputed ‘off’ times at previous visits

MI ignoring treatment

As ‘MI accounting for treatment’ excluding treatment from the model

MI placebo only

As ‘MI accounting for treatment’ with apomorphine patients assumed to receive placebo after premature discontinuation

Table S1. Breakdown of patients by country according to treatment group (full analysis set).

Country (n of centres), n (%)			
Austria (3)	7 (13.0%)	5 (9.3%)	12 (11.2%)
Denmark (1)	1 (1.9%)	2 (3.7%)	3. (2.8%)
France (3)	7 (13.0%)	4 (7.4%)	11 (10.3%)
Germany (4)	10 (18.5%)	10 (18.5%)	20 (18.7%)
Netherlands (3)	7 (13.0%)	7 (13.0%)	14 (13.1%)
Spain (5)	12 (22.2%)	14 (25.9%)	26 (24.3%)
United Kingdom (4)	9 (16.7%)	11 (20.4%)	20 (18.7%)

Table S2. Anti-PD medications at baseline and Week 12.

Anti-PD drug category	Apomorphine		Placebo	
	Baseline (n=54)	Week 12 (n=54)	Baseline (n=53)	Week 12 (n=53)
Levodopa-containing drug	54	53	53	53
Dopamine agonist	48	28	43	38
MOA-B inhibitor	23	19	21	21
Amantadine	16	13	13	13
Total*	141	113	130	125

*Patients can be in more than one row. Includes patients who discontinued the double-blind phase early; these had their last visit assigned to Week 12.

Table S3. Summary of efficacy findings at Week 12 (full analysis set) – post hoc analyses.

Change from baseline to Week 12	Apomorphine (n=53)	Placebo (n=53)	Treatment difference (95% CI)	p-value
Absolute change in time spent 'On' without dyskinesia (h/day)	3.06	1.09	-1.97 (0.67, 3.27)	0.0018
Absolute change in time spent 'On' with non-troublesome dyskinesia (h/day)	-0.29	-0.29	-0.00 (-1.02, 1.01)	0.6066
Absolute change in time spent 'On' with troublesome dyskinesia (h/day)	-0.24	-0.09	-0.15 (-0.79, 0.48)	0.4682

Table S4. Frequency of patients experiencing ‘on’ time with troublesome dyskinesia at baseline (full analysis set).

On with troublesome dyskinesia at baseline (hours)	Frequency (FAS)	Cumulative Frequency
0	54	54
0.25	3	57
0.5	4	61
0.75	5	66
1	4	70
1.25	3	73
1.5	3	76
1.75	4	80
2	2	82
2.25	1	83
2.5	3	86
2.75	3	89
3	4	93
3.25	4	97
3.5	3	100
4.5	1	101
4.75	1	102
5.5	2	104
5.75	1	105
6.75	1	106

Table S5. Mean levodopa-equivalent dose at baseline and Week 12 by drug category (safety set).

Anti-PD drug category	Levodopa-equivalent dose (mg) mean (SD)			
	Apomorphine		Placebo	
	Baseline (n=54)	Week 12 (n=54)	Baseline (n=53)	Week 12 (n=53)
Levodopa-containing drug	1055.1 (656.03)	812.5 (419.24)	1105.7 (543.76)	993.8 (417.51)
Dopamine agonist	347.4 (277.13)	203.6 (151.69)	277.9 (137.72)	247.8 (119.78)
MOA-B inhibitor	94.0 (20.60)	97.4 (11.47)	97.6 (10.91)	97.6 (10.91)
Amantadine	200.0 (81.65)	200.0 (91.29)	250.0 (95.74)	250.0 (95.74)

Table S6. Summary of exploratory efficacy and safety endpoints evaluated in the study.

Efficacy endpoints

- Change in Score of the Non-Motor Symptoms Scale for PD
- Change in MDS-UPDRS Part I patient questionnaire (non-motor experiences of daily living)
- Change in MDS-UPDRS II, assessed separately for ‘on’ and ‘off’ states
- Change in MDS-UPDRS Part IV fluctuations
- Drop-outs due to lack of efficacy
- Beck Depression Scale
- PDSS (PD Sleep Scale)

Safety endpoints:

- Evaluation of adverse events and local tolerability
- Skin changes
- Full blood count
- Epworth Sleepiness Scale
- QUIP
- C-SSRS (Columbia-Suicide Severity Rating Scale)

Table S7. Summary of adverse events (AE) at Week 12 (safety set) showing Clopper–Pearson exact confidence intervals (%).

Values are n (%)	Apomorphine (n=54)	Placebo (n=53)
At least one treatment-emergent AE (TEAE)	50 (92.6%) (82.11–97.94)	30 (56.6%) (42.28–70.16)
Most common TEAE (≥10% of patients)		
Skin nodules at infusion site	24 (44.4%) (30.92–58.6)	0 (0–5.50)
Mild	20 (37.0%) (24.29–51.26)	0 (0–5.50)
Moderate	4 (7.4%) (2.06–17.89)	0 (0–5.50)
Nausea	12 (22.2%) (12.04–35.6)	5 (9.4%) (3.13–20.66)
Mild	10 (18.5%) (9.25–31.43)	3 (5.7%) (1.18–15.66)
Moderate	2 (3.7%) (0.45–12.75)	2 (3.8%) (0.46–12.98)
Somnolence	12 (22.2%) (12.04–35.6)	2 (3.8%) (0.46–12.98)
Mild	5 (9.3%) (3.08–20.3)	1 (1.9%) (0.05–10.07)
Moderate	6 (11.1%) (4.19–22.63)	1 (1.9%) (0.05–10.07)
Severe	1 (1.9%) (0.05–9.89)	0 (0–5.50)
Infusion site erythema	9 (16.7%) (7.92–29.29)	2 (3.8%) (0.46–12.98)
Mild	8 (14.8%) (6.62–27.12)	2 (3.8%) (0.46–12.98)
Moderate	1 (1.9%) (0.05–9.89)	0 (0–5.50)
Dyskinesia	8 (14.8%) (6.62–27.12)	0 (0–5.50)
Mild	5 (9.3%) (3.08–20.3)	0 (0–5.50)

Moderate	3 (5.6%) (1.16–15.39)	0 (0–5.50)
Headache	7 (13.0%) (5.37–24.9)	2 (3.8%) (0.46–12.98)
Mild	6 (11.1%) (4.19–22.63)	2 (3.8%) (0.46–12.98)
Moderate	1 (1.9%) (0.05–9.89)	0 (0–5.50)
Insomnia	6 (11.1%) (4.19–22.63)	1 (1.9%) (0.05–10.07)
Mild	2 (3.7%) (0.45–12.75)	0 (0–5.50)
Moderate	4 (7.4%) (2.06–17.89)	1 (1.9%) (0.05–10.07)
At least one AE with a local intolerability (skin changes at injection site)	32 (59.3%) (45.03–72.43)	8 (15.1%) (6.75–27.59)
Severe AES	8 (14.8%) (6.62–27.12)	2 (3.8%) (0.46–12.98)
Serious AEs	5 (9.3%) (3.08–20.3)	2 (3.8%) (0.46–12.98)
AEs leading to study discontinuation	6 (11.1%) (4.19–22.63)	0 (0–5.50)
AEs leading to dose modification	26 (48.1%) (34.34–62.16)	6 (11.3%) (4.27–23.03)

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