Apomorphine subcutaneous infusion in patients with Parkinson's disease with persistent motor fluctuations (TOLEDO): a multicentre, double-blind, randomised, placebo-controlled trial

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Summary

Background Subcutaneous apomorphine infusion is a clinically established therapy for patients with Parkinson's disease with motor fluctuations not optimally controlled by oral medication. Open-label studies have shown that apomorphine infusion is effective in reducing off time (periods when antiparkinsonian drugs have no effect), dyskinesias, and levodopa dose, but confirmatory evidence from double-blind, controlled studies is lacking. We aimed to investigate the efficacy and safety of apomorphine infusion compared with placebo in patients with Parkinson's disease with persistent motor fluctuations despite optimised oral or transdermal treatment.

Methods In this randomised, placebo-controlled, double-blind, multicentre trial, we enrolled patients at 23 European hospitals who had been diagnosed with Parkinson's disease more than 3 years previously and had motor fluctuations not adequately controlled by medical treatment. Patients were randomly assigned (1:1) with a computer-generated randomisation code, stratified by site, to receive 3–8 mg/h apomorphine or placebo saline infusion during waking hours (16 h a day [range 14–18 was acceptable]) for 12 weeks. The flow rate of the study drug and other oral medications could be adjusted during the first 4 weeks on the basis of individual efficacy and tolerability, after which patients entered an 8-week maintenance period. The primary endpoint was the absolute change in daily off time based on patient's diaries, and was assessed in the full analysis set, which was defined as all patients who received at least one dose of allocated study drug and had efficacy data available at any timepoint post-baseline. Safety was assessed in all patients who received at least one dose of apomorphine or placebo. All study participants and investigators were masked to treatment assignment. Both the 12-week double-blind phase and the 52-week open-label phase of this study are now complete; this paper reports results for the double-blind phase only. This study is registered with ClinicalTrials.gov (NCT02006121).

Findings Between March 3, 2014, and March 1, 2016, 128 patients were screened for eligibility and 107 were randomly assigned, of whom 106 were included in the full analysis set (n=53 in both groups). Apomorphine infusion (mean final dose 4·68 mg/h [SD 1·50]) significantly reduced off time compared with placebo (–2·47 h per day [SD 3·70] in the apomorphine group *vs* –0·58 h per day [2·80] in the placebo group; difference –1·89 h per day, 95% CI –3·16 to –0·62; p=0·0025). Apomorphine was well tolerated without any unexpected safety signals. Six patients in the apomorphine group withdrew from the study because of treatment-related adverse events.

Interpretation Apomorphine infusion results in a clinically meaningful reduction in off time in patients with Parkinson's disease with persistent motor fluctuations despite optimised oral or transdermal therapy.

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Introduction

Parkinson's disease is characterised by neurodegeneration of the substantia nigra, resulting in progressive striatal dopamine deficiency and motor symptoms.[1] Dopamine replacement therapy is effective, but most patients eventually experience motor fluctuations as the disease progresses. These are typically managed by shortening the intervals between levodopa intakes, increasing levodopa dose, adding selective monoamine oxidase type B (MAOB) inhibitors and catechol-O-methyltransferase (COMT) inhibitors to prolong dopamine availability, or using oral or transdermal dopamine agonists.[2] Over time, motor fluctuations usually worsen, leading to long and troublesome periods of immobility and non-motor symptoms, and attempts to control fluctuations with oral medication can lead to disabling dyskinesia. Persistent motor complications can be managed with deep brain stimulation or continuous dopaminergic drug delivery using either subcutaneous infusion of the dopamine agonist apomorphine or intestinal infusion of levodopa-carbidopa gel. High-level evidence supports

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Research in context

Evidence before this study

The long-term management of Parkinson's disease is often 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 patients with Parkinson's disease whose motor fluctuations have not been adequately controlled by oral medication. Since that time, it has been used in clinical practice in many countries. To investigate the evidence base for apomorphine infusion, we searched PubMed up to Feb 1, 2014, without language restrictions and using the search terms "apomorphine" and "infusion". Although the efficacy of intermittent apomorphine injection therapy has been shown in randomised studies, evidence for apomorphine infusion has only come from uncontrolled, open-label studies. To our knowledge, no randomised, controlled studies of apomorphine infusion have been done since our search of the literature.

Added value of this study

To our knowledge, the TOLEDO study is the first randomised, double-blind, placebo-controlled trial to investigate the efficacy, safety, and tolerability of apomorphine subcutaneous infusion in patients with Parkinson's disease whose motor fluctuations are uncontrolled despite optimised oral or transdermal therapy. The study is an important addition to the evidence base for apomorphine infusion, for which high-level evidence is currently lacking.

Implications of all the available evidence

Apomorphine infusion can provide a significant and clinically meaningful reduction in off time without increasing dyskinesias, and is an effective and well tolerated treatment strategy for patients with Parkinson's disease whose motor fluctuations are uncontrolled despite optimised oral or transdermal therapy. The treatment effect in our study was of the same magnitude as that observed for intestinal levodopa-carbidopa gel infusion in the only other large, randomised study of an infusion therapy in patients with Parkinson's disease, and exceeded that seen with oral or transdermal medication when tested in the setting of a placebo-controlled, randomised trial. Additionally, continuous infusion of apomorphine might allow for a reduction in the required doses of concomitant oral antiparkinsonian medications.

the efficacy of deep brain stimulation and levodopa-carbidopa gel, but both treatments are invasive and associated with certain risks.[3]

Apomorphine is a potent dopamine receptor agonist with affinity for all dopamine receptor subtypes.[4] It was first licensed in the UK for use in the treatment of Parkinson's disease in 1993 on the basis of findings from an open-label, comparative study[5] that showed that apomorphine had equivalent antiparkinsonian efficacy to levodopa, and it remains the only available medication with the same symptomatic efficacy as levodopa. Subcutaneous apomorphine infusion is currently licensed for severe motor fluctuations, and is reimbursed by several health-care systems across the world. Numerous short-term and long-term uncontrolled studies have shown the efficacy of apomorphine in reducing off time (namely, when the patient's medication is not working optimally, and parkinsonian symptoms return), with reductions of up to 80% reported, and most have also shown 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, which is an important weakness in the formal evidence base for this treatment option.

Here we present the results of the 12-week, double-blind phase of the TOLEDO study, which aimed to investigate the efficacy and safety of apomorphine subcutaneous infusion in patients with Parkinson's disease.

For the **TOLEDO study protocol** see https://www.britannia-pharm.co.uk/uploads/TOLEDO-Protocol-Final-clean-3-0-20140702.pdf

Methods

Study design

TOLEDO was a prospective, multicentre, phase 3 study of apomorphine subcutaneous infusion compared with placebo in patients with Parkinson's disease with persistent motor fluctuations despite optimised oral or transdermal medication. The trial included a 12-week, parallel-group, double-blind, placebo-controlled phase (figure 1), followed by a 52-week open-label phase.

Participants were enrolled at 23 university and general hospitals specialised in the treatment of Parkinson's disease in Austria, Denmark, France, Germany, Spain, the Netherlands, and the UK. Eligible participants were aged 30 years or older, had been diagnosed with Parkinson's disease more than 3 years previously according to the Queen Square Brain Bank criteria (except that patients with more than one first-degree affected relative were allowed),[8] and had levodopa-related motor fluctuations that had not been adequately controlled by optimised medical treatment (defined as containing four or more daily doses of levodopa and judged to be optimal by an investigator). Patients' Hoehn and Yahr stage had to be 3 or less in the on state and 2–5 in the off state. Patients were required to have been on the same dose of oral medication for 4 weeks or more before enrolment and to be able to differentiate between their subjective on and off states and between on with troublesome or non-troublesome dyskinesia and on

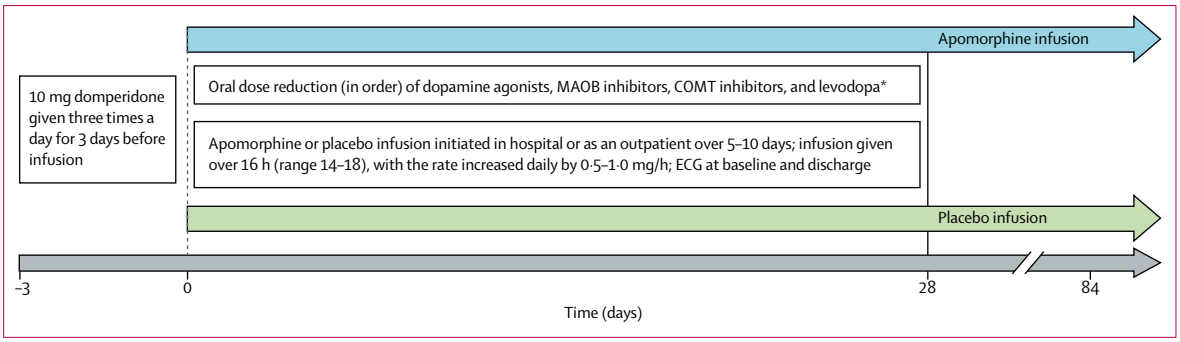

Figure 1: **TOLEDO study design (12-week double-blind phase)**
Following completion of a 12-week, parallel-group, double-blind, placebo-controlled phase, or in case of withdrawal because of lack of efficacy of study drug, patients could enter a 52-week open-label phase. MAOB=monoamine oxidase type B. COMT=catechol-O-methyl transferase. ECG=electrocardiogram. *Both the dose and frequency of oral levodopa were reduced.

without dyskinesia, and to document those states in their diaries. Additionally, eligible patients had to have a mean of 3 h or more off time per day for 2 days based on diaries at screening and baseline, with no day with less than 2 h off time recorded.[9] All oral or transdermal antiparkinsonian drugs available in the participating countries were permitted, except for budipine.

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

Apomorphine has been licensed and clinically used in all the included countries for many years. Apart from mandated titration and prohibited use of bolus dosing during the double-blind period, the trial design closely resembled routine clinical practice. This low-risk study design negated the need for a data safety monitoring board, but the trial was overseen by a steering committee of neurologists who were specialists in Parkinson's disease and had extensive experience in apomorphine infusion.

TOLEDO was conducted in accordance with the International Conference on Harmonization Good Clinical Practice guidelines and the Declaration of Helsinki.[10] 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.

Randomisation and masking

Eligible patients were randomly assigned in a 1:1 ratio within a block size of four to either apomorphine or placebo subcutaneous infusion using a central, computer-generated randomisation code generated by the Biometric Department of Advanced Medical Services, Mannheim, Germany, using SAS software version 9.4. Randomisation was stratified by site.

We used Clincase (Quadratek Data Solutions, Berlin, Germany) as the electronic data capture system. All study participants and investigators were masked to group assignment. 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) scores[11] and Patient Global Impression of Change (PGIC) scores.[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 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.

Procedures

Apomorphine subcutaneous infusion was provided in 10 mL pre-filled glass syringes (Catalent Pharma Solutions, Brussels, Belgium) and delivered as a 5 mg/mL solution for infusion with a CRONO APO-go infusion pump (Canè, Turin, Italy). 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 with the same pump system.

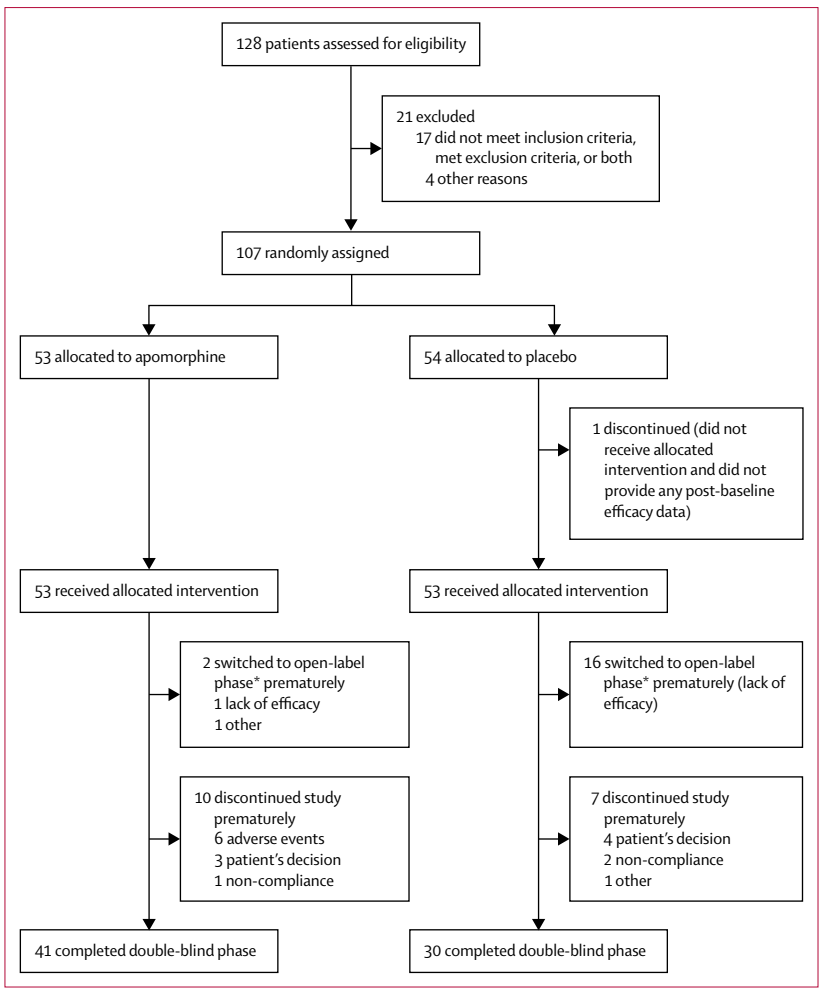

Figure 2: **Trial profile**
*In the open-label phase, all patients received apomorphine infusion.

The target dose of apomorphine was each patient's individual optimised dose at hourly flow rates of 3–8 mg, administered for roughly 16 h of their waking day. Infusion times of 14–18 h were permissible, and any shorter duration (minimum 12 h) required an explanation by the investigator. Treatment was started during a hospital stay that lasted 5–10 days, during which patients and carers received infusion-system training. In centres where outpatient titration was already standard practice, treatment could be started during 5–10 day-case admissions. Antiemetic pre-medication was administered according to local standards and the investigator's judgement. For domperidone, the recommended dose was 10 mg given at most three times a day and starting 3 days before infusion.[13] On day 1, patients received a starting dose of study drug at a flow rate of 1 mg/h. During the inpatient or day-case dose-adjustment period, the flow rate could be adjusted daily by 0·5–1·0 mg/h, after which it could be adjusted weekly up to the end of week 4 and up to a maximum of 8 mg/h or until the highest tolerated dose was reached, whichever occurred first. To be discharged, patients had to be receiving 3 mg/h or more.

Any reductions in concomitant medications for Parkinson's disease 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 to reduce and discontinue oral or transdermal dopamine agonists first, followed by MAOB inhibitors. For levodopa or combined levodopa and COMT, doses were to be reduced first, followed by an increase in the intervals between doses. COMT inhibitors could be discontinued. Amantadine and anticholinergics were left unchanged. The titration period was followed by an 8-week maintenance period during which the dose of apomorphine was unchanged. Use of the bolus function of the pump was not permitted, and levodopa rescue doses for off periods were limited to 300 mg per day during the titration phase and 200 mg per day during the maintenance phase. Patients who developed nocturnal off periods after discontinuation of controlled-release dopamine agonists could be re-started on that agonist up to the original dose at bedtime.

Patients visited the hospital 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 2 days before baseline, each day during the inpatient or day-case stay, and 2 days before each visit at weeks 2, 3, 4, 6, and 12, patients completed 24 h home diary assessments of motor status at 30 min intervals, recording periods when they were on, off, and sleeping. We also assessed vital signs and did safety assessments at each visit. Clinical variables were measured at baseline, at the end of hospital stay, and then monthly with standard haematology and biochemistry laboratory tests.

After completing the 12-week double-blind phase, or in the case of withdrawal due to lack of efficacy of study drug, patients could enter the 52-week open-label phase of the trial, during which all patients received apomorphine infusion.

Outcomes

The primary efficacy endpoint was the absolute change in off time (derived from patient's diaries) from baseline to the week 12 visit. Secondary efficacy endpoints were response to therapy, defined as an off time reduction of 2 h or more from baseline; PGIC scores; absolute change in on time without troublesome dyskinesia; change in oral levodopa dose and levodopa-equivalent dose;[14] change in MDS-UPDRS Part III (motor examination) scores during on periods; and change in quality of life, as assessed with the 8-item Parkinson's Disease Questionnaire (PDQ-8).[15] Safety assessments included evaluation of adverse events and local tolerability; clinical and laboratory variables; electrocardiograms; and scores on the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's disease

(long version),[16] the Epworth Sleepiness Scale,[17] and the Columbia Suicide Severity Rating Scale.[18] Severe adverse events were defined according to Good Clinical Practice as significant impairment of functioning (the patient is unable to carry out usual activities, the patient's life is at risk from the event, or both).

Statistical analysis

Sample size was calculated on the basis of previous experience and a review of the published data, and assuming that a mean off time of 6·5 h at baseline would be reduced to 3·5 h with apomorphine and to 5 h with placebo.[19,20] We estimated that 34 patients in each group would provide 90% power, with a two-sided significance of 5%, to detect a treatment effect of 1·5 h, assuming a SD of 1·75 h for the apomorphine group and 2·5 h for the placebo group. A conservative estimate of 30% unavailable patients (due to very early dropout or poor completion of patient diaries) was made, and so we aimed to enrol 102 patients, which provided an additional 5% of patients to allow for a non-parametric statistical test.

All randomised patients who received at least one dose of study drug and had efficacy data for any timepoint post-baseline were included in the efficacy analysis (full analysis set). Missing data for the primary endpoint were imputed with last observation carried forward. Sensitivity analyses were done with imputation of post-titration (after week 4 visit) values only, with fitting of a mixed model for repeated measurements (MMRM) that assumed missing data were missing at random, and with multiple imputation. Descriptive safety data are based on the safety dataset, which comprised all patients who received at least one dose of any study drug.

A planned blinded interim analysis confirmed the assumptions used for sample size calculations but could not rule out potentially harmful worsening of symptoms in placebo-treated patients due to increased off time. The sponsor subsequently chartered Clintrex (Longboat Key, FL, USA) to act as an independent data review committee. Clintrex reviewed data for 76 randomised patients, found no undue risk, and recommended continuation of the study as planned. Direct data transfer between the unblinded Clinical Research Organisation staff and Clintrex meant no study staff were exposed to unblinded data.

Except for the sensitivity analyses, the Wilcoxon rank-sum 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 sensitivity analyses, MMRM used the difference in least-squares means and multiple imputation used ANCOVA. Statistical analyses were done with SAS version 9.4. Tests with a two-sided significance level of less than 5% are defined as significant. No adjustment has been made for multiplicity.

This study is registered with ClinicalTrials.gov (NCT02006121).

	Apomorphine (n=53)	Placebo (n=53)
Sex		
Men	34 (64%)	32 (60%)
Women	19 (36%)	21 (40%)
Age (years)	63·6 (9·3)	63·0 (8·3)
<65 years	26 (49%)	29 (55%)
≥65 years	27 (51%)	24 (45%)
Disease duration (years)	11·8 (5·6)	10·6 (4·3)
Daily levodopa dose (mg)	920·4 (518·7)	989·0 (461·4)
Daily levodopa-equivalent dose (mg)	1485·5 (702·6)	1472·6 (567·9)
Off time (h per day)	6·69 (2·23)	6·76 (2·51)
On time without troublesome dyskinesia (h per day)	8·52 (2·36)	8·56 (2·39)
MDS-UPDRS Part III score during on periods	30·6 (13·65)	28·02 (15·25)
PDQ-8 score	32·67 (15·03)	31·01 (12·66)
Country		
Austria	7 (13%)	5 (9%)
Denmark	1 (2%)	2 (4%)
France	7 (13%)	4 (8%)
Germany	10 (19%)	10 (19%)
Netherlands	7 (13%)	7 (13%)
Spain	12 (23%)	14 (26%)
UK	9 (17%)	11 (21%)
Antiparkinsonian medication		
Levodopa-containing drug	53 (100%)	53 (100%)
Dopamine agonist	48 (91%)	42 (79%)
MAOB inhibitor	23 (43%)	20 (38%)
COMT inhibitor	32 (60%)	33 (62%)
Amantadine	16 (30%)	12 (23%)

Data are n (%) or mean (SD). MDS-UPDRS=Movement Disorder Society Unified Parkinson's Disease Rating Scale. PDQ-8=8-item Parkinson's Disease Questionnaire. MAOB=monoamine oxidase type B.

Table 1: **Baseline characteristics (full analysis set)**

Role of the funding source

The funder of the study participated in study design, provided funding for editorial and formatting assistance (under corresponding author direction), and was responsible for data collection, monitoring, and statistical analysis. All authors had full access to all data in the study 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 March 3, 2014, and March 1, 2016, 128 patients were screened for eligibility, of whom 107 were randomly assigned to apomorphine (n=53) or to placebo (n=54). Post-baseline efficacy data were not available for one patient in the placebo group and so 106 patients were included in the full analysis set (53 in both groups; figure 2). Of those patients, 71 completed all 12 weeks of the double-blind phase of the study (41 in the

	Apomorphine (n=53)	Placebo (n=53)	Treatment difference (95% CI)	p value
Primary outcome				
Off time (h per day)	–2·47 (3·70)	–0·58 (2·80)	–1·89 (–3·16 to –0·62)	0·0025
Secondary outcomes				
Number of patients with ≥2 h reduction in off time	33 (62%)	15 (29%)	33·4% (15·5 to 51·4)	0·0008
PGIC score	3·23 (1·42)	4·43 (1·10)	–1·20 (–1·71 to –0·69)	<0·0001
On time without troublesome dyskinesia (h per day)	2·77 (3·26)	0·80 (2·93)	1·97 (0·69 to 3·24)	0·0008
Oral levodopa dose (mg)	–207·8 (439·5)	–94·3 (273·4)	–113·5 (–262·3 to 35·2)	0·0615
Levodopa-equivalent dose (mg)	–492·1 (618·3)	–163·7 (367·5)	–328·5 (–535·2 to –121·7)	0·0014
MDS-UPDRS Part III motor scores during on periods	–3·42 (11·69)	–0·89 (9·73)	–2·52 (–7·53 to 2·48)	0·4642
PDQ-8 score	–0·06 (14·37)	2·40 (11·83)	–2·47 (–7·62 to 2·69)	0·3971

Data are n (%) or mean (SD) unless otherwise specified. PGIC=Patient Global Impression of Change. MDS-UPDRS=Movement Disorder Society Unified Parkinson's Disease Rating Scale. PDQ-8=8-item Parkinson's Disease Questionnaire.

Table 2: **Change between baseline and week 12 in efficacy outcomes (full analysis set)**

apomorphine group and 30 in the placebo group; figure 2) and 35 (12 in the apomorphine group and 23 in the placebo group) did not complete all 12 weeks but contributed diary data to the primary efficacy analysis. 36 patients discontinued the double-blind phase before week 12, including 12 in the apomorphine group (two switched early to the open-label phase and ten discontinued the study) and 23 in the placebo group (16 switched early to the open-label phase and seven discontinued the study; figure 2). The most common reasons for discontinuation of the double-blind phase were adverse events in the apomorphine group (n=6) and lack of efficacy in the placebo group (n=16). Demographic variables were balanced across the treatment groups at baseline, as was use of anti-parkinsonian medications (table 1; appendix). The mean final dose of study drug was 4·68 mg/h (SD 1·50) in the apomorphine group and 5·76 mg/h (1·79) in the placebo group.

See Online for appendix

Patients who received active apomorphine infusions had significantly greater reductions in off times at week 12 than did patients who received placebo infusions. A significant reduction in off time with apomorphine infusion was observed at 12 weeks: the mean change from baseline to week 12 in off time was –2·47 h per day (SD 3·70) for the apomorphine group and –0·58 h per day (2·80) for the placebo group (treatment difference –1·89 h per day, 95% CI –3·16 to –0·62; p=0·0025; table 2, figure 3A, B). These results were consistent across prespecified subgroups of sex and age (<65 years *vs* ≥65 years) and in sensitivity analyses (appendix). 33 (62%) of 53 patients who received apomorphine had a 2 h or more reduction in off time at week 12 compared with 15 (29%) of 53 patients who received placebo (treatment difference 33·4%, 95% CI 15·5–51·4; p=0·0008; table 2).

Compared with placebo, apomorphine significantly increased on time without troublesome dyskinesia: absolute mean change was 2·77 h per day (SD 3·26) in the apomorphine group and 0·80 h per day (2·93) in the placebo group (treatment difference 1·97 h per day, 95% CI 0·69–3·24; p=0·0008; table 2, figure 3C). Apomorphine infusion also significantly improved PGIC scores at week 12 compared with placebo (p<0·0001; table 2, figure 4). At week 12, 34 (71%) of 48 patients in the apomorphine group thought that their general health state was improved compared with nine (18%) of 51 patients in the placebo group (figure 4).

The mean reduction in oral levodopa dose from baseline to week 12 was greater in the apomorphine group than in the placebo group, although the difference between the treatment groups was not significant (p=0·0615; table 2). However, the reduction in oral levodopa-equivalent dose between baseline and week 12 was significantly greater in the apomorphine group than in the placebo group (p=0·0014; table 2), and this difference was significant at all visits from week 4 (figure 5). Mean levodopa-equivalent doses at baseline and week 12 by drug category are shown in the appendix. Change in quality of life between baseline and week 12, as assessed with PDQ-8 scores and MDS-UPDRS Part III motor scores during on periods, was not significantly different between the treatment groups (table 2).

Post-hoc analyses of absolute change in on time without dyskinesia, with non-troublesome dyskinesia, and with troublesome dyskinesia are shown in figure 3A. The frequency of patients experiencing troublesome dyskinesia at baseline is also shown in the appendix.

Apomorphine infusion was well tolerated and no unexpected safety signals were observed (table 3). Most events were mild or moderate in intensity, and no deaths occurred during the study. Overall, 50 (93%) of 54 patients in the apomorphine group had at least one treatment-emergent adverse event compared with 30 (57%) of 53 patients in the placebo group. The most common adverse events were skin reactions, nausea, and somnolence. A greater proportion of patients in the apomorphine group than in the placebo group experienced an adverse event that required dose

modification. A summary of adverse events at week 12 for the safety set showing Clopper-Pearson exact confidence intervals is in the appendix.

Six patients, all in the apomorphine group, had an adverse event that led to study withdrawal. Three patients withdrew because of serious adverse events: one had severe hypotension, one had myocardial infarction, and one had persistently abnormal haematology test results indicating mild leucopenia and moderate anaemia (with 9·5 mg as the lowest recorded haemoglobin level), but was not found to be haemolytic. The three remaining patients withdrew because of experiencing visual hallucination (n=1), moderate gait disturbance (n=1), or mild infusion-site erythema (n=1). All adverse events leading to study withdrawal, except for myocardial infarction, were thought to be treatment related, and all were resolved after cessation of study drug.

Serious adverse events occurred in five patients in the apomorphine group (table 3); in addition to the three cases that led to study withdrawal, there was one case of severe intermittent confusion (resolved on dose reduction) and one of severe infusion-site cellulitis (resolved). Two patients in the placebo group had a serious adverse event, including one with severe depression and one with colitis.

Neuropsychiatric adverse events in the apomorphine group included one case of mild hypersexuality (resolved on dose reduction), two cases of mild punding (one resolved and the other not resolved; in each case the apomorphine dose was not changed), three episodes of confusion in a single patient (two mild and one severe; all resolved on dose reduction), one case of moderate psychosis (resolved without dose change), and two cases of hallucinations (one mild that resolved without dose change and one moderate that resolved after cessation of the study drug). In the placebo group, there were three reported episodes of mild confusion (in two patients) and two cases of mild hallucinations (all resolved).

There were no clinically significant differences between groups in Epworth Sleepiness Scale scores; Columbia Suicide Severity Rating Scale scores; responses on the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease; and biochemistry, haematology, and vital signs (data not shown).

Discussion

We found that, compared with placebo, apomorphine subcutaneous infusion provided a significant reduction in off time in patients with Parkinson's disease who were experiencing persistent motor fluctuations despite adjustments in their oral or transdermal medication. Importantly, this improvement was not achieved at the expense of worsening dyskinesias.

The mean difference in off time between the apomorphine and placebo groups was almost 2 h, and a similar effect size was seen for the change in on time without troublesome dyskinesia. Although 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 reported

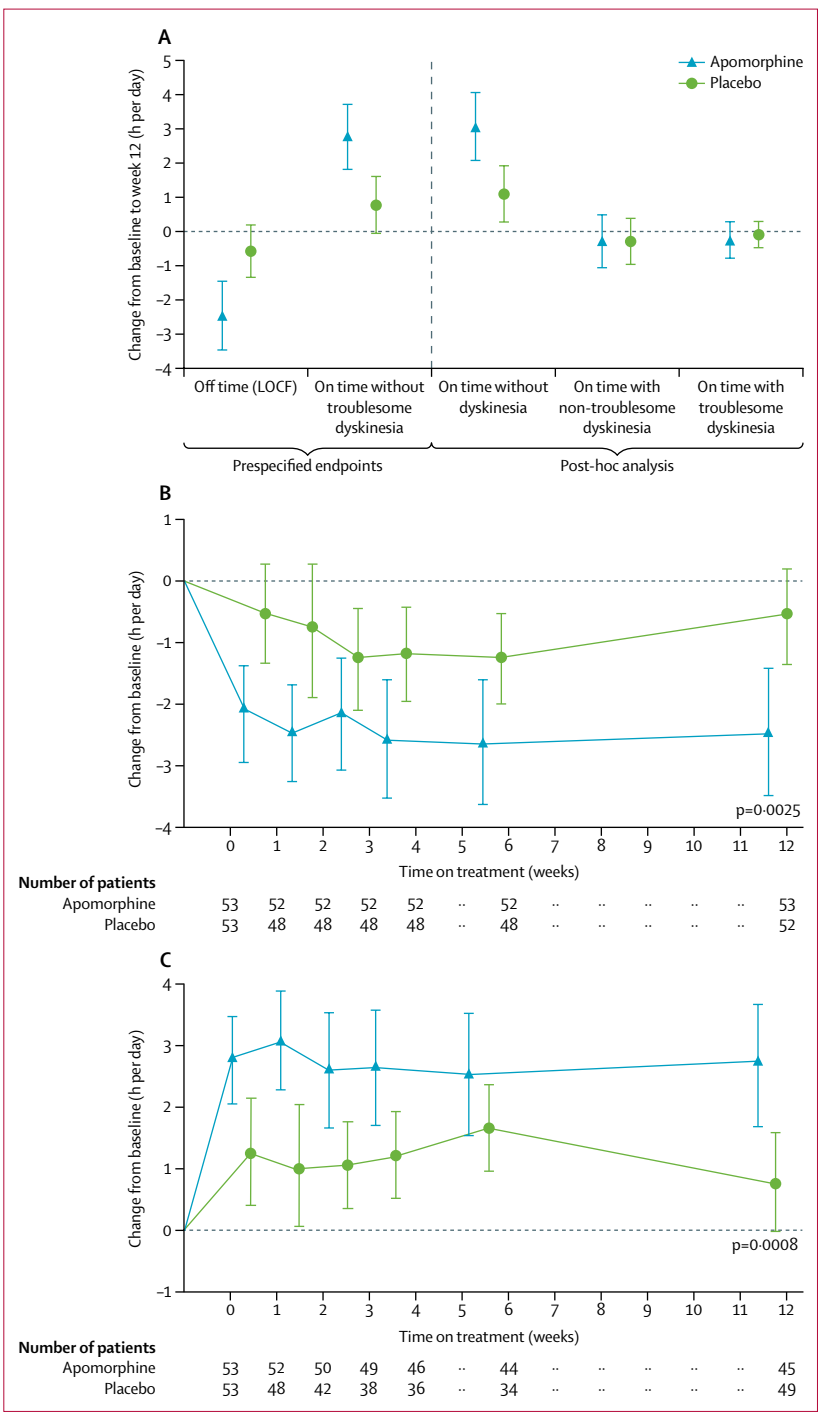

Figure 3: **Change in efficacy endpoints from baseline to week 12 (full analysis set)**
Error bars indicate 95% CIs. (A) Mean change in various motor states of Parkinson's disease between baseline and week 12; on without troublesome dyskinesia is the combination of on without dyskinesia and on with non-troublesome dyskinesia. (B) Change from baseline to week 12 in off time (LOCF); each point is the mean of the values for the two consecutive days before the visit. (C) Change from baseline to week 12 in time spent on without troublesome dyskinesia; each point is the mean of the values for the two consecutive days before the visit. LOCF=last observation carried forward.

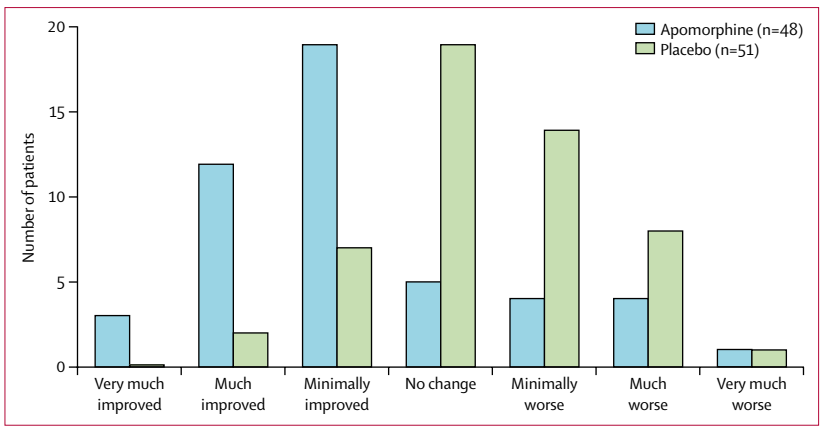

Figure 4: **Patient Global Impression of Change from baseline to week 12 (full analysis set)**

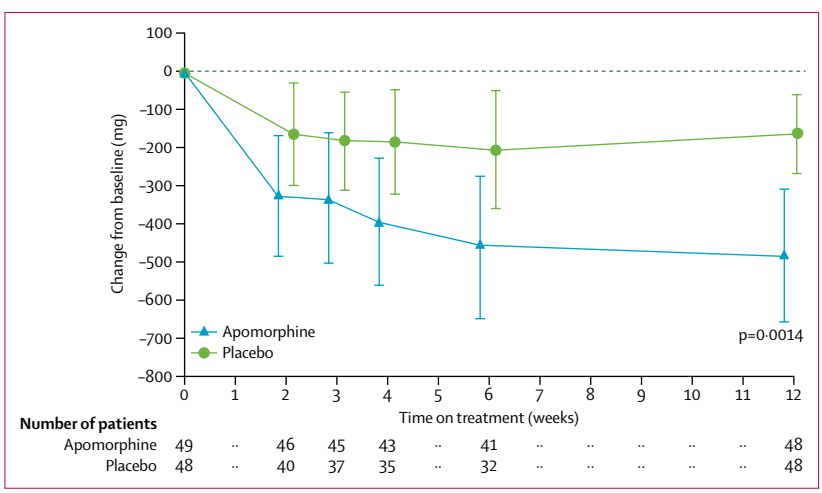

Figure 5: **Mean change in levodopa-equivalent dose from baseline to week 12 (full analysis set*)**
Error bars indicate 95% CIs. *Analysis excludes as-needed use and missing data from three sites.

in open-label studies,[7] and the majority (62%) of patients treated with apomorphine achieved 2 h or more 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 two times the change in off time identified as clinically meaningful to patients.[22]

The clinical relevance of these results was highlighted by PGIC scores: significantly more patients in the apomorphine group than in the placebo group rated themselves as improved. Apomorphine infusion was also associated with a significant reduction in the requirement for concomitant 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 probably clinically relevant to patients with motor complications because it might 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 motor complications of Parkinson's disease, including use of device-aided treatments for persistent motor fluctuations, which are only considered when patients have received all other options without tangible benefit. Patients' baseline characteristics, including antiparkinsonian medications, were similar to those reported in previous studies[2,23] of treatments for persistent motor complications. Dissimilar to the TOLEDO study, in a randomised controlled trial[23] of levodopa-carbidopa gel, COMT inhibitors and slow-release levodopa preparations were discontinued before randomisation (replaced with immediate-release and intestinal levodopa), which allowed treatment optimisation in all participants (due to the double-dummy design), resulting in greater levodopa doses at final visits compared with baseline in both groups.

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

Reports of adverse events and tolerability were in line with those in previous observational studies,[4,6] with most patients treated with apomorphine experiencing at least one adverse event during the study. All six adverse events that led to study withdrawal occurred in the apomorphine group, of which five were thought to be possibly related to treatment. However, none had a sustained negative effect, and all were reversed on cessation of treatment. The only reported case of severe infusion-site reaction resolved without leading to study withdrawal. Somnolence occurred in 12 patients in the apomorphine group, but was severe in only one patient, despite around half of the patients randomly assigned to apomorphine receiving concomitant treatment with an oral dopamine agonist. Neuropsychiatric adverse events occurred more commonly in the apomorphine group than in the placebo group, but almost all were 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 in practice. 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 investigated here. Additionally, although most patients started treatment as inpatients, outpatient initiation of treatment was also possible, which, depending on the health-care system and circumstances, might mean more convenience to patients and health-care providers and a reduced need for use of inpatient hospital resources.

TOLEDO was not powered to assess an anti-dyskinetic effect of apomorphine infusion, which has been observed in many open-label studies.[7] Time spent on without

troublesome dyskinesia increased significantly in the apomorphine group compared with the placebo group, but, as in the randomised study of levodopa-carbidopa intestinal gel,[23] baseline dyskinesia severity was reasonably low, which might explain the lack of a significant change in existing dyskinesias. Dyskinesias were reported as an adverse event in eight patients treated with apomorphine; however, five of these were in the dose-adjustment phase in which dyskinesias were used as a trigger for oral dose reduction.

This study has some limitations. First, 36 patients did not complete the full 12-week, double-blind phase, of whom 18 switched into the open-label phase early, including 16 patients in the placebo group. For 17 patients, this switch was due to lack of study drug efficacy. We had expected that the number of patients choosing to switch early would be higher in the placebo group than in the apomorphine group, and this finding might be considered an indirect indicator of the efficacy of apomorphine. Nevertheless, the unequal loss of participants from the groups might have caused a degree of attrition bias. However, offering patients the option of switching to open-label apomorphine infusion was considered necessary for ethical reasons because the study was done in countries where apomorphine is part of standard clinical management.

Second, 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 might have contributed to the adverse events.

Third, 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 affected blinding. Although patients were required to have been previously untreated with apomorphine infusion, use of apomorphine injections in the past was allowed so as to reflect the population who would normally be offered apomorphine infusion. Although the onset of clinical effect is slower with infusion than with injection, and the dose was increased gradually, it is conceivable that familiarity with the drug's effects might have occurred. Moreover, the MDS-UPDRS scores were assessed by physicians, whose familiarity with the effects of apomorphine might have affected blinding.

Finally, the short study duration might have precluded opportunities for observation of 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, physicians aim to reduce doses of oral medications to a greater extent when dyskinesias are a concern, and maximum dyskinesia reduction might take up to several months.[24] The reasonably short dose-adjustment period and overall study duration, as well as the insufficient power of the study, might also explain why a significant effect on patient quality of life was not observed, despite the significant benefit of apomorphine on PGIC scores. A positive effect on quality of life has otherwise been quite consistently shown in open-label studies[25–27] of apomorphine infusion, including in longer-term and multicentre studies. Shorter-term (12–18 weeks) randomised trials[28,29] of other efficacious antiparkinsonian medications have also failed to detect changes on quality-of-life scales. 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.

	Apomorphine (n=54)	Placebo (n=53)
At least one treatment-emergent adverse event	50 (93%)	30 (57%)
Treatment-emergent adverse events*		
Skin nodules at infusion site	24 (44%)	0
Mild	20 (37%)	0
Moderate	4 (7%)	0
Nausea	12 (22%)	5 (9%)
Mild	10 (19%)	3 (6%)
Moderate	2 (4%)	2 (4%)
Somnolence	12 (22%)	2 (4%)
Mild	5 (9%)	1 (2%)
Moderate	6 (11%)	1 (2%)
Severe	1 (2%)	0
Infusion site erythema	9 (17%)	2 (4%)
Mild	8 (15%)	2 (4%)
Moderate	1 (2%)	0
Dyskinesia	8 (15%)	0
Mild	5 (9%)	0
Moderate	3 (6%)	0
Headache	7 (13%)	2 (4%)
Mild	6 (11%)	2 (4%)
Moderate	1 (2%)	0
Insomnia	6 (11%)	1 (2%)
Mild	2 (4%)	0
Moderate	4 (7%)	1 (2%)
At least one adverse event with local intolerability (skin changes at injection site)	32 (59%)	8 (15%)
Severe adverse events	8 (15%)	2 (4%)
Serious adverse events	5 (9%)	2 (4%)
Adverse events leading to study discontinuation	6 (11%)	0
Adverse events leading to dose modification	26 (48%)	6 (11%)

Data are n (%). *Only treatment-emergent adverse events that occurred in ≥10% of patients in each group are shown.

Table 3: **Summary of adverse events by week 12 (safety set)**

In summary, apomorphine infusion has beneficial clinical effects on motor fluctuations in patients with Parkinson's disease that persist despite optimisation of oral or transdermal medication. Additionally, continuous subcutaneous administration of apomorphine might allow the dose and number of doses of short-acting oral antiparkinsonian medication to be reduced. Although no comparative, randomised studies of apomorphine versus levodopa-carbidopa gel have yet been done, both infusion treatments have similar effect sizes,[28] and apomorphine infusion is easily reversible and less invasive than levodopa-carbidopa gel, 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 patients with Parkinson's disease 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 from the patient's perspective. We hope that treatment guidelines will be developed to guide physicians, and apomorphine infusion will be offered and reimbursed more widely as an effective treatment option.

Contributors

The TOLEDO Steering Committee (RK, AL, WP, OR, CT, and GD, plus representatives of the sponsor) developed the study. RK, WP, OR, and CT contributed to trial design, data acquisition, data interpretation, and writing of the report. GD and AL contributed to trial design, data interpretation, and writing of the report. KRC, TH, and TvL contributed to data acquisition, data interpretation, and writing of the report. KS was responsible for trial oversight and contributed to data acquisition, data interpretation, and writing of the report. SV was responsible for medical oversight and contributed to data interpretation and writing of the report. HS was responsible for the statistical analysis and interpretation of results. All authors approved the final draft of the manuscript.

Declaration of interests

RK reports personal fees, non-financial support, and grants from Britannia Pharmaceuticals during the conduct of the study, and personal fees, grants, and non-financial support from AbbVie, Acorda, Adamas, AOP Orphan, Bial, Biotie, Britannia Pharmaceuticals, Cynapsus, Global Kinetics Corporation, Grünenthal, Licher, Novartis, Stada, UCB, and Zambon outside the submitted work. WP reports personal fees from Britannia Pharmaceuticals during the conduct of the study, and personal fees from AbbVie, AstraZeneca, Bial, Biogen, Cynapsus, Britannia Pharmaceuticals, Grünenthal, Intec, Ipsen, Lundbeck, Merz Pharmaceuticals, Novartis, NeuroDerm, Orion Pharma, Prexton, Teva, UCB, and Zambon outside the submitted work. OR reports personal fees from Britannia Pharmaceuticals during the conduct of the study. OR also reports grants from Agence Nationale de la Recherche, Centre Hospitalier Universitaire de Toulouse, France-Parkinson, INSERM (French National Institute of Health and Medical Research), Michael J Fox Foundation, Programme Hospitalier de Recherche Clinique, and European Commission, and acted as a scientific advisor for AbbVie, Adamas, Acorda, Addex, AlzProtect, Apopharma, Astrazeneca, Bial, Biogen, Britannia Pharmaceuticals, Clevexel, Cynapsus, INC Reasearch, Lundbeck, Merck, MundiPharma, NeuroDerm, Novartis, Oxford Biomedica, Parexel, Pfizer, Prexton Therapeutics, Quintiles, Sanofi, Servier, Teva, UCB, XenoPort, and Zambon, outside the submitted work. CT reports personal fees from Britannia Pharmaceuticals during the conduct of the study. CT also reports grants from the Michael J Fox Foundation, the European Commission Horizon 2020 Program (Propag-Ageing), MundiPharma, and Vifor; acting as a scientific advisor for Britannia Pharmaceuticals, Novartis, UCB, MundiPharma, Vifor, Benevolent, Orion Pharma, Pfizer; speaker's honoraria from Grünenthal, UCB, and AbbVie, outside the submitted work. GD reports lecture fees from Boston Scientific and Novartis, and has served as a consultant for Boston Scientific. He receives funding for his research from the German Research Council, the German Ministry of Education and Research, and Medtronic. KRC reports personal fees from Britannia Pharmaceuticals, during the conduct of the study, and has received consultancy fees from Britannia Pharmaceuticals, UCB, AbbVie, Otsuka, Mundipharma, Zambon, Profile, Bial, Sunovion, Merz, Pfizer, and Roche, outside the submitted work. KRC has also been an advisor to UCB, Bial, AbbVie, Merz, Sunovion, Zambon, Britannia Pharmaceuticals, Airliquid, and Jazz Pharma, and Pfizer, outside the submitted work. He has also received grants from the EU, EU Horizon 2020, Parkinson's UK, Medical Research Council (MRC) UK, MRC Singapore, National Parkinson Foundation, Kirby Laing Foundation, National Institute of Health Research (NIHR), and NIHR Biomedical Research Centres, outside the submitted work. TH reports grants from Britannia Pharmaceuticals, during the conduct of the study, and has received honoraria for lectures from Britannia Pharmaceuticals, UCB, Nordic Infucare, Zambon, Grünenthal, and AbbVie, outside the submitted work. TvL reports honoraria for lectures from Britannia Pharmaceuticals, grant support from Lysosomal Therapeutics, lecture fees from AbbVie and UCB, and honoraria for participation in an advisory board from Neuroderm. KS and SV report being employed by Britannia Pharmaceuticals during the conduct of the study. HS reports consultancy fees from Britannia Pharmaceuticals. AL reports consultancy fees from Britannia Pharmaceuticals and Bial, and honoraria from Profile Pharmaceuticals, Teva, Lundbeck, Nordiclnfu Care, NeuroDerm, UCB, and Roche, outside the submitted work.

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 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.

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