Apomorphine sublingual film for off episodes in Parkinson's disease: a randomised, double-blind, placebo-controlled phase 3 study

C Warren Olanow, Stewart A Factor, Alberto J Espay, Robert A Hauser, Holly A Shill, Stuart Isaacson, Rajesh Pahwa, Mika Leinonen, Parul Bhargava, Ken Sciarappa, Bradford Navia*, David Blum, for the CTH-300 Study investigators†*

Summary

Background Many patients with Parkinson's disease have potentially disabling off episodes that are not predictably responsive to levodopa. In this study, we assessed the safety and efficacy of apomorphine sublingual film as an on-demand therapy for off episodes in patients with Parkinson's disease.

Methods This randomised, double-blind, placebo-controlled study was done by movement disorder specialists at 32 sites in the USA and one in Canada. Patients with Parkinson's disease who had 2 h or more of off time per day with predictable morning off periods, were responsive to levodopa, and were on stable doses of anti-parkinsonian medication were eligible. In an open-label titration phase, increasing doses of apomorphine sublingual film (10–35 mg) were administered until a tolerable full on response was achieved. Patients were then randomly assigned (1:1) with an interactive web-response system to receive the effective dose of apomorphine sublingual film or matching placebo in a 12-week, double-blind maintenance phase. Randomisation was not stratified, and the block size was four. All patients and study personnel were masked to treatment assignments. The primary endpoint was the in-clinic change from predose to 30 min post-dose in the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part 3 (motor) score at week 12, analysed on a modified intention-to-treat population by use of a mixed-effect model for repeated measures. Safety analyses were done on all enrolled patients who received at least one dose of study medication. This trial is registered with ClinicalTrials.gov, NCT02469090.

Findings Between June 18, 2015, and Dec 11, 2017, 109 patients were enrolled and randomly assigned to receive apomorphine sublingual film (n=54) or placebo (n=55). All patients received the assigned study treatment, and 34 (63%) of 54 patients receiving apomorphine sublingual film and 46 (84%) of 55 receiving placebo completed the study. Least squares mean (SE) change from predose to 30 min post-dose in MDS-UPDRS part 3 score at week 12 was –11·1 (SE 1·46, 95% CI –14·0 to –8·2) with apomorphine sublingual film and –3·5 (1·29, –6·1 to –0·9) with placebo (difference –7·6, SE 1·96, 95% CI –11·5 to –3·7; p=0·0002). Mild-to-moderate oropharyngeal events were the most common side-effect, reported in 17 (31%) of 54 patients receiving apomorphine sublingual film and in four (7%) of 55 patients receiving placebo, leading to treatment discontinuation in nine (17%) patients treated with apomorphine and in one (2%) patient treated with placebo. Other treatment-emergent adverse events were transient nausea (in 15 [28%] patients receiving apomorphine sublingual film), somnolence (seven [13%]), and dizziness (five [9%]). Orthostatic hypotension, syncope, dyskinesia, hallucinations, prolongation of the QT interval, and impulse control disorders were infrequent (prevalence ≤2% of all patients) or did not occur. One patient treated with apomorphine sublingual film (with known cardiac risk factors) had a fatal cardiac arrest.

Interpretation Although nearly a third of patients discontinued treatment primarily because of oropharyngeal side-effects, apomorphine sublingual film provided an efficacious, on-demand treatment for off episodes for most patients with Parkinson's disease in this trial. The long-term safety and efficacy of apomorphine sublingual film are currently being investigated.

Funding Cynapsus Therapeutics and Sunovion.

Lancet Neurol 2020; 19: 135–44

Published Online December 6, 2019 https://doi.org/10.1016/S1474-4422(19)30396-5

See Comment page 105

*Contributed equally

†Collaborators listed in the appendix

Department of Neurology, Icahn School of Medicine at Mount Sinai, New York, NY, USA (Prof C W Olanow MD); **Clintrex, Sarasota, FL, USA** (Prof C W Olanow, M Leinonen MSc); **Department of Neurology, Emory University, Atlanta, GA, USA** (Prof S A Factor DO); **Department of Neurology and Rehabilitation Medicine, University of Cincinnati, Cincinnati, OH, USA** (Prof A J Espay MD); **Department of Neurology, University of South Florida, Tampa, FL, USA** (Prof R A Hauser MD); **Barrow Neurological Institute, Phoenix, AZ, USA** (H A Shill MD); **Parkinson's Disease and Movement Disorders Center of Boca Raton, Boca Raton, FL, USA** (S Isaacson MD); **University of Kansas Medical Center, University of Kansas, Kansas City, KS, USA** (Prof R Pahwa MD); **and Sunovion, Marlborough, MA, USA** (P Bhargava PhD, K Sciarappa PhD, B Navia MD, D Blum MD)

Correspondence to: Prof C Warren Olanow, Department of Neurology, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA **warren.olanow@clintrex.com**

See Online for appendix

Introduction

Parkinson's disease is the second most common neurodegenerative disorder, after Alzheimer's disease, affecting approximately 1 million people in north America.[1] 50 years after its introduction, levodopa remains the most effective treatment for the motor features of this disease. However, chronic levodopa treatment is associated with the development of motor complications (motor fluctuations and dyskinesias) that frequently begin within 1–2 years after initiation of therapy and ultimately affect as many as 90% of patients.[2–4] Surveys of patients with Parkinson's disease indicate that motor fluctuations are perceived as a greater problem than dyskinesias,[5] although many patients might be

Research in context

Evidence before this study

We searched PubMed for clinical trials published in English up to April 24, 2019, with the search terms "apomorphine", "sublingual", "Parkinson's disease", "Parkinson", "motor fluctuations", "motor complications", "off periods", "off episodes", and "off state". The search yielded eight studies assessing various formulations of sublingual apomorphine. In a phase 2, open-label, proof-of-concept study, 19 patients with Parkinson's disease in the practically defined off state (anti-parkinsonian medication withheld overnight for approximately 12 h) were titrated with apomorphine sublingual film (APL-130277; 10–30 mg) in 5-mg increments until a full on response was achieved. Most patients (80%) achieved a full on response within 30 min, with a mean duration of on response of 50 min (SD 19·4). There were no discontinuations due to adverse events. Sublingual apomorphine seemed to provide a rapid and reliable method for treating off episodes in patients with Parkinson's disease.

Added value of this study

Our study supports earlier findings that apomorphine sublingual film is an efficacious on-demand treatment for off episodes for most patients with Parkinson's disease who were able to tolerate treatment. Apomorphine sublingual film met the primary endpoint (change from predose to 30 min post-dose in the Movement Disorder Society Unified Parkinson's Disease Rating Scale part 3 [motor] score at week 12) and the key secondary endpoint (percentage of patients who achieved a full on response within 30 min post-dose at week 12) of the study. Oropharyngeal events were the most common treatment-related side-effect leading to discontinuation; however, these adverse events were mild to moderate in severity.

Implications of all the available evidence

A rapid and reliable on-demand therapy for off episodes is an important therapeutic need in the management of Parkinson's disease. Subcutaneous apomorphine is an approved therapy for this indication but requires an injection and is not widely used. Inhaled levodopa was approved in the USA in 2018, but has a dose limitation and requires co-administration of carbidopa. Apomorphine sublingual film provides an additional option for the on-demand treatment of off episodes in most patients with Parkinson's disease who tolerate the therapy.

undertreated for fear of higher levodopa doses causing dyskinesia.

Motor fluctuations are characterised by a cycle in which patients have a period of drug responsiveness (on response) followed by a return of parkinsonian features before the onset of benefit from the subsequent dose (off episode).[6] Off episodes can manifest as parkinsonism with tremor, rigidity, bradykinesia, gait impairment, and falling, as well as non-motor features such as pain, anxiety, and depression; these can be disabling for patients and greatly affect their quality of life.[6–10] Additionally, with chronic levodopa treatment and advanced disease, the response to a given dose of levodopa can become unpredictable, and patients might have a loss of benefit from one dose before the onset of benefit from the subsequent dose (end-of-dose wearing off), a delayed response (delayed on response), a partial response (partial on response), a dose failure (no on response), and unpredictable and rapid changes between the on and off states (on-off phenomenon).[7,11,12] Furthermore, patients can be troubled by off episodes upon waking (early-morning akinesia). Despite the availability of several medical and surgical treatments to reduce daily off time, many patients still have off episodes that are troubling and do not predictably respond to a dose of levodopa. This uncertainty can cause patients to become depressed, withdrawn, and unwilling or unable to engage in social activities.

Two approved treatment options are available for the on-demand management of off episodes in patients with Parkinson's disease: a subcutaneous administration of apomorphine, which is available in most countries, and inhaled levodopa, which was approved in 2018 by the US Food and Drug Administration. Apomorphine is a potent, non-ergoline dopamine agonist with anti-parkinsonian benefits similar to levodopa. Subcutaneous administration of apomorphine has been shown to be an effective rescue treatment for individual off episodes.[13–17] However, despite its robust anti-parkinsonian effects, subcutaneous apomorphine has not been widely accepted by the Parkinson's disease community because of difficulty with product assembly, the need for a subcutaneous injection and initial titration supervised in clinic, potentially severe dopaminergic side-effects, and the frequent development of skin nodules and ulcerations at injection sites.[14–18]

To address the practical limitations of subcutaneous apomorphine, a novel sublingual formulation of the drug has been developed (APL-130277). This formulation is composed of a soluble bilayer film containing apomorphine in one layer and a pH-controlling buffer in the other.[19] The apomorphine sublingual film is placed under the tongue and is designed to deliver apomorphine systemically through absorption from the oral cavity mucosa, thus bypassing the extensive first-pass metabolism associated with gastrointestinal administration of the compound. In an open-label study of 19 patients with Parkinson's disease complicated by off episodes, apomorphine sublingual film was well tolerated and most patients achieved a full on response within 30 min, which was maintained throughout a 90-min evaluation period.[20] These results suggest that apomorphine sublingual film might offer a safe and effective alternative on-demand treatment for individual off episodes without some of the problems associated with subcutaneous injections. In this study, we report the results of the first double-blind, placebo-controlled study

that aimed to assess the safety and efficacy of apomorphine sublingual film as an on-demand therapy for off episodes in patients with Parkinson's disease.

Methods

Study design and participants

This study was a randomised, double-blind, placebo-controlled, multicentre phase 3 trial and was done at 32 academic neurology centres in the USA and one in Canada (appendix p 4). Each site screened at least one patient. The protocol, patient information, consent form, and other relevant study documentation were approved by an institutional review board at each study site, and written informed consent was obtained from all patients before study initiation. The study was done in accordance with the International Conference on Harmonisation Guideline for Good Clinical Practice and the Declaration of Helsinki.

Patients with a diagnosis of Parkinson's disease consistent with UK Brain Bank criteria[21] who were responsive to levodopa, had at least 2 h of off time per day with predictable morning off periods, and were receiving stable doses of anti-parkinsonian medication were eligible to participate. Exclusion criteria included atypical or secondary parkinsonism, previous surgical treatment for Parkinson's disease, clinically significant oral pathology, and clinically significant medical, surgical, psychiatric, or laboratory abnormalities in the judgment of the study investigator. Eligibility also required review and approval by an independent enrolment adjudication committee before randomisation. Full eligibility criteria are provided in the appendix (p 2).

Randomisation and masking

Patients were randomly assigned (1:1) to receive treatment with either apomorphine sublingual film at the tolerated dose that provided a full on response during titration or an identical matching placebo. Randomisation was done by use of an interactive web-response system, was not stratified, and the block size was four. A computer-generated random allocation was used by the vendor responsible for the interactive web-response system and corresponded with the sequentially numbered foil pouches of study medication. For each dose, active and placebo study medication and packaging were identical in size, shape, colour, and appearance. All patients and study personnel were masked to treatment assignments.

Procedures

Our study included an open-label titration phase folowed by a 12-week double-blind maintenance phase (appendix p 1). During titration and maintenance phase visits, patients arrived at the clinic in a practically defined off state (anti-parkinsonian medication withheld overnight for approximately 12 h), received the apomorphine sublingual film administered by trained staff, and were specifically instructed not to swallow for 3 min, because

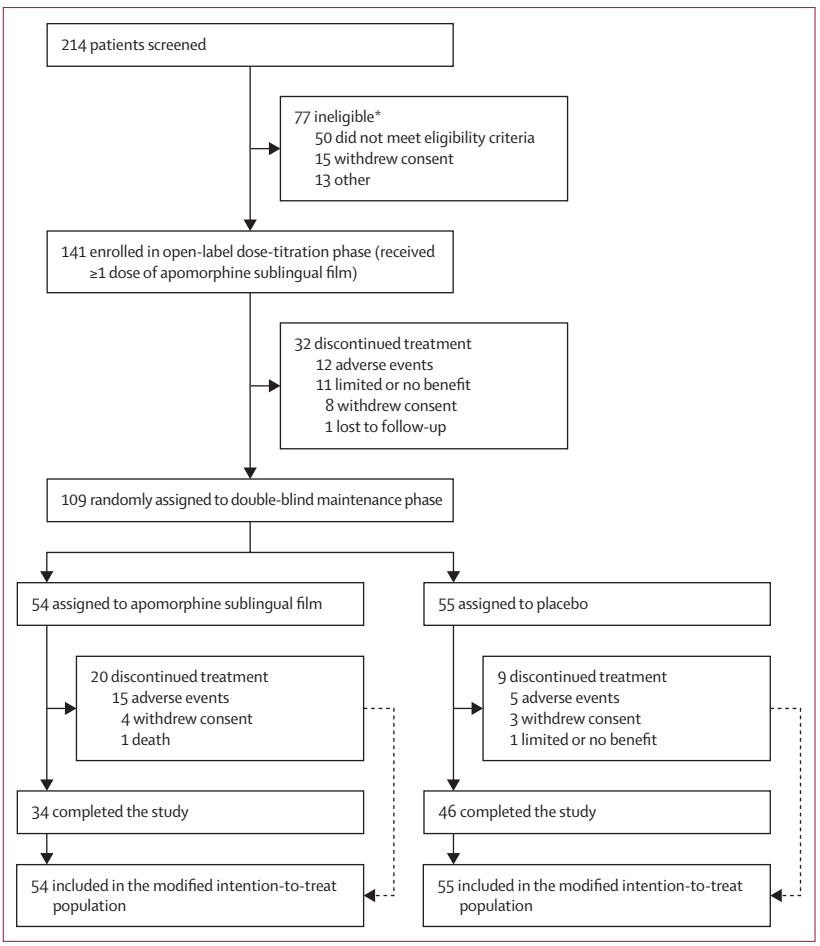

Figure 1: **Trial profile**
*Patients can be included in more than one category of ineligibility.

apomorphine is rapidly sulfonated in the stomach and is not absorbed. Titration started with a 10 mg dose of apomorphine sublingual film, which could be increased on subsequent days in 5 mg increments to a maximum of 35 mg until a full on response was achieved within 45 min without intolerable side-effects. A full on response was defined as an on response similar to that obtained with levodopa.

During the maintenance phase, efficacy assessments were done at the clinic in patients in a practically defined off state at the random assignment visit (week 0) and at weeks 4, 8, and 12. Assessments at each visit included part 3 (motor examination) of the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS)[22] done predose and at 15, 30, 45, 60, and 90 min post-dose, the complete MDS-UPDRS, Patient Global Impression of Improvement (PGI-I), Clinical Global Impression of Improvement (CGI-I), the 39-item Parkinson's Disease Questionnaire (PDQ-39), the Epworth Sleepiness Scale (ESS), and European Quality of Life–5 Dimensions questionnaire (EQ-5D). Patients were also directed to self-administer the study drug during the maintenance phase

	Apomorphine sublingual film (n=54)	Placebo (n=55)
Age (years)	62·9 (9·79)	62·5 (8·12)
Sex		
Men	37 (69%)	31 (56%)
Women	17 (31%)	24 (44%)
Race		
White	50 (93%)	51 (93%)
Other	4 (7%)	4 (7%)
Time since diagnosis (years)	8·7 (4·25)	9·3 (3·84)
Time since motor fluctuations started (years)	4·7 (3·92)	4·5 (3·78)
On state modified Hoehn and Yahr score		
1 or 1·5	0	1 (2%)
2 or 2·5	49 (91%)	42 (76%)
3	5 (9%)	11 (20%)
Missing	0	1 (2%)
MDS-UPDRS part 3 (predose)*	43·2 (15·17)	43·1 (14·38)
Number of off episodes per day	3·9 (1·17)	3·8 (1·40)
Type of off episode		
Morning akinesia	46 (85%)	44 (80%)
Wearing off	54 (100%)	54 (98%)
Delayed on	29 (54%)	43 (78%)
Dose failure	22 (41%)	23 (42%)
Sudden off	26 (48%)	32 (58%)
Self-rated full on response rate within 30 min post-dose	37 (69%)	41 (75%)
Total daily levodopa dose (mg)	1059 (563)	1008 (562)
Concomitant Parkinson's disease medications		
Levodopa-containing agents	54 (100%)	55 (100%)
Dopamine agonists	30 (56%)	31 (56%)
Monoamine oxidase B inhibitors	22 (41%)	24 (44%)
Amantadine	8 (15%)	16 (29%)
Catechol-O-methyltransferase inhibitors	5 (9%)	5 (9%)

Data are n (%) or mean (SD). MDS-UPDRS=Movement Disorder Society Unified Parkinson's Disease Rating Scale. *Baseline score refers to the predose MDS-UPDRS part 3 score at the baseline visit (last titration visit at which the randomised dose was given).

Table 1: **Baseline characteristics of the modified intention-to-treat population**

at home for the treatment of up to five off episodes per day. A home-dosing diary was completed during the 2 days before each visit, in which the patient recorded the time of each study drug administration and whether a full on response was achieved at 30 min post-dose.

Throughout the study, patients were maintained on their standard anti-parkinsonian medications. Anti-nausea medication (trimethobenzamide 300 mg three times per day at US sites or domperidone 10 mg two times per day at the Canadian site) was administered for 3 days before initiation of titration and could subsequently be discontinued during the maintenance phase at the discretion of the investigator.

Outcomes

The primary endpoint was the mean change from predose to 30 min post-dose in the MDS-UPDRS part 3 score at the 12-week visit, which was assessed locally by an investigator at each site. The key secondary endpoint was the percentage of patients with a self-rated full on response within 30 min at the 12-week visit. Other secondary endpoints in hierarchical order were the percentage of patients at week 12 who had a full on response within 30 min post-dose with a duration of benefit of at least 30 min, improvement in PGI-I at week 12, improvement in CGI-I at week 12, change from baseline to week 12 in MDS-UPDRS part 2, full on response of treated episodes at 30 min post-dose in the home environment on the basis of the home-dosing diary, mean change from baseline to week 12 in PDQ-39 summary index score, mean change in MDS-UPDRS part 3 from predose to 15 min post-dose at week 12, and time to medication effect at week 12. Additional patient-reported secondary endpoints included mean change from baseline to week 12 in ESS and EQ-5D.

Safety assessments were done at each titration and maintenance visit and at the end of study visit. These included assessment of treatment-emergent adverse events, serious adverse events, vital signs, electrocardiograms, the Columbia Suicide Severity Rating Scale (C-SSRS), and a specific oropharyngeal cavity examination. Additionally, the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale (QUIP-RS) was assessed at each maintenance visit and at the end of study visit.

Statistical analysis

We estimated that a sample size of 44 patients per group, completing the double-blind maintenance phase, would provide at least 90% power to detect a mean treatment difference of 7 points in the MDS-UPDRS part 3 score change, assuming an SD of 10 points and a two-sided 5% significance level. We assumed a 10% dropout during the titration phase and a 15% dropout during the maintenance phase.

Analysis of the primary endpoint was done using a mixed-effect model for repeated measures (MMRM). The MMRM included the observed outcomes at weeks 0, 4, 8, and 12 as response values; the treatment group, visit, and interaction between treatment group and visit as fixed factors; and the change in MDS-UPDRS part 3 score between predose and 30 min post-dose at the titration visit, at which the randomised dose was administered, as a covariate. We also did prespecified sensitivity analyses for the primary endpoint including MMRM for the completer population (defined as all patients in the modified intention-to-treat population who had a valid MDS-UPDRS part 3 score at predose and after 30 min post-dose at baseline and the maintenance visit at 12 weeks) and per-protocol population (defined as all patients in the modified intention-to-treat population who completed the study with no major protocol deviation), multiple imputation

	Hierarchy	Apomorphine sublingual film (n=54)	Placebo (n=55)	Effect size (95% CI)*	p value†
MDS-UPDRS part 3 score change from predose to 30 min post-dose at week 12	1 (primary endpoint)	–11·1 (–14·0 to –8·2)	–3·5 (–6·1 to –0·9)	Difference –7·6 (–11·5 to –3·7)	0·0002
Response rate of self-rated full on response within 30 min at week 12	2 (key secondary endpoint)	35% (21 to 53)	16% (8 to 30)	OR 2·81 (1·04 to 7·64)	0·043
Secondary endpoints					
Response rate of self-rated full on response within 30 min post-dose with effect lasting for at least 30 min at week 12	3†	31% (18 to 48)	14% (7 to 27)	OR 2·80 (1·00 to 7·84)	0·050
PGI-I improved‡ at week 12	4	20 (37%)	11 (20%)	..	0·062
CGI-I improved‡ at week 12	5	22 (41%)	11 (20%)	..	0·027
MDS-UPDRS part 2 score change from baseline to week 12	6	0·995 (–0·559 to 2·549)	2·095 (0·749 to 3·440)	Difference –1·100 (–3·159 to 0·959)	0·29
Full on response rate at week 12, percentage of treated episodes at 30 min post-dose based on home-dosing diary§	7	79% (64·2 to 93·2)	31% (19·3 to 43·0)	Difference 47·6 (28·8 to 66·4)	<0·0001
PDQ-39 summary index score change from baseline to week 12 (mean [95% CI])	8	0·309 (–2·748 to 3·366)	–1·671 (–4·442 to 1·101)	Difference 1·979 (–2·162 to 6·120)	0·34
MDS-UPDRS part 3 score change from predose to 15 min post-dose at week 12 (mean [95% CI])	9	–6·4 (–8·8 to –4·0)	–3·0 (–5·1 to –0·8)	Difference –3·4 (–6·7 to –0·2)	0·039
Time to medication effect at week 12 (min; median [95% CI])	10	21·2 (15·0 to 27·0)	NE¶ (42·7 to NE)	HR 3·4‖ (1·99 to 5·69)	<0·0001
Patient-reported secondary endpoints					
ESS total score at week 12 (mean change [SD])	NA	0·5 (3·2; n=34)	–0·6 (3·9; n=45)	..	..
EQ-5D VAS score at week 12 (mean change [SD])	NA	–3·8 (17·7; n=34)	0 (26·0; n=44)	..	..
EQ-5D index score at week 12 (mean change [SD])	NA	–0·0319 (0·1371; n=34)	–0·0004 (0·2272; n=45)	..	..

Data are n (%), % (95% CI), or LSM (95% CI), unless specified otherwise. MDS-UPDRS=Movement Disorder Society Unified Parkinson's Disease Rating Scale. LSM=least squares mean. OR=odds ratio. PGI-I=Patient Global Impression of Improvement. CGI-I=Clinical Global Impression of Improvement. PDQ-39=39-item Parkinson's Disease Questionnaire. NE=not estimable. HR=hazard ratio. ESS=Epworth Sleepiness Scale. NA=not applicable. EQ-5D=European Quality of Life—5 Dimensions. VAS=Visual Analogue Scale.
*Data are treatment differences, estimated OR, or estimated HR. †The p values shown after the third endpoint are nominal and not adjusted for multiplicity. ‡Very much improved, much improved, or minimally improved; in the case of missing data, the patient was considered not improved. §Based on self-completed home-dosing diary done in an outpatient setting. ¶Median and 95% CI were not estimable because fewer than 50% of patients treated with placebo had medication effect by 90 min. ‖HR was estimated by use of a Cox proportional hazards model.

Table 2: **Primary, secondary, and patient-reported endpoints in rank order according to hierarchical testing in the modified intention-to-treat population**

analyses with missing-at-random and missing-not-at-random (placebo-based imputation and tipping point-based imputation) assumptions, responder analysis based on MDS-UPDRS part 3 scores, and last observation carried forward using an ANCOVA model. We analysed continuous secondary endpoints using the MMRM similar to that used for the primary endpoint; for the analysis of categorical secondary endpoints, we used a generalised linear mixed model (with logit link function) for binomial data. The model included the observed outcomes at weeks 0, 4, 8, and 12 as response values; treatment group, visit, and interaction between treatment group and visit as fixed factors; and the baseline assessment as a covariate. We tested each endpoint within the hierarchy sequentially and we considered them statistically significant if the p value was $p<0·05$ and the preceding endpoint in the hierarchy was significant. Once a p value was $p>0·05$, we no longer considered subsequent analyses to be statistically significant; we present nominal p values after the first non-significant result only for descriptive purposes.

All efficacy analyses were done in the modified intention-to-treat population, defined as all patients who were randomly assigned and received at least one post-randomisation dose of study medication. The safety population consisted of all enrolled patients who received at least one dose of study medication. A data safety monitoring board reviewed the safety data. We used SAS (version 9.3 or higher) for all statistical analyses. This trial is registered with ClinicalTrials.gov, NCT02469090.

Role of the funding source

The funder of the study was responsible for data collection, monitoring, and statistical analysis. The authors were responsible for the study design, statistical plan, interpretation of data, writing the manuscript, and decision to publish. Upon request, all authors had full access to the database, could do independent statistical analyses, and could verify the completeness and accuracy of the data and analyses. The corresponding author had final responsibility for the decision to submit for publication.

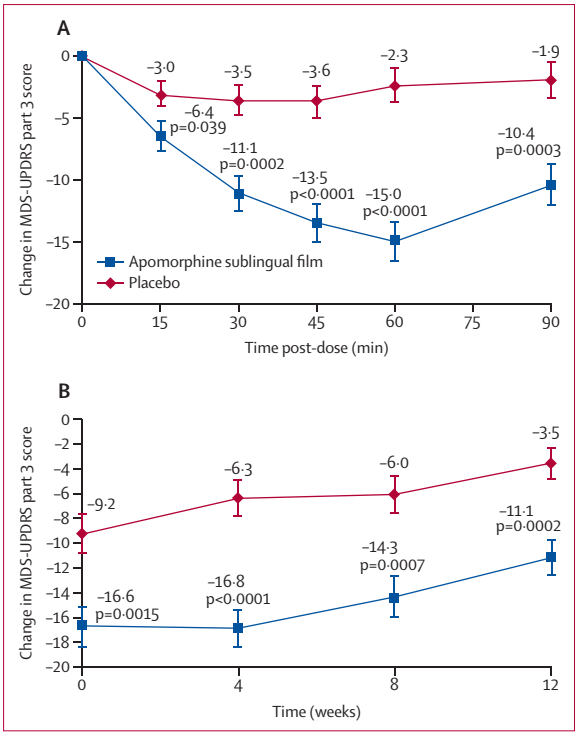

Figure 2: **Changes in MDS-UPDRS part 3 motor examination score in the modified intention-to-treat population**
Data are least squares means (SE). (A) Change from predose (time 0) to 15 min, 30 min, 45 min, 60 min, and 90 min post-dose at week 12 for both treatment groups. The 30-min timepoint represents the primary endpoint. (B) Change from predose to 30 min post-dose at the randomisation visit (week 0) and at study visits at weeks 4, 8, and 12. MDS-UPDRS=Movement Disorder Society Unified Parkinson's Disease Rating Scale.

Results

Between June 18, 2015, and Dec 11, 2017, 214 patients were assessed for eligibility. Of these, 141 (66%) patients were enrolled in the open-label titration phase and received at least one dose of apomorphine sublingual film (figure 1). 32 patients discontinued during the titration phase, including 12 patients who withdrew because of adverse events. 109 (77%) patients were then randomly assigned to receive apomorphine sublingual film (n=54) or placebo (n=55). The doses of apomorphine sublingual film administered at randomisation that resulted in a full on response during titration were: 10 mg (20 [18%] of 109 patients), 15 mg (29 [27%]), 20 mg (23 [21%]), 25 mg (21 [19%]), 30 mg (nine [8%]), and 35 mg (seven [6%]). Baseline characteristics were similar between treatment groups (table 1). At baseline, patients had a mean of 3·9 off episodes per day (SD 1·3) and were taking a mean dose of levodopa of 1033 mg per day (SD 560·78). The baseline mean MDS-UPDRS part 3 score was 43·1 (SD 14·7), and 78 (72%) of 109 patients had a self-rated full on response within 30 min post-dose at their last titration visit.

The change (SE) from predose to 30 min post-dose in MDS-UPDRS part 3 score at week 12 (the primary endpoint) was significantly greater in patients who received apomorphine sublingual film than in patients treated with placebo (change –11·1, SE 1·46, 95% CI –14·0 to –8·2, with apomorphine sublingual film *vs* –3·5, 1·29, –6·1 to –0·9, with placebo), with a least squares mean difference of –7·6 (SE 1·96, 95% CI –11·5 to –3·7; p=0·0002; table 2). We observed separation from placebo at week 12 for all measured post-dose timepoints, from 15 min to 90 min (figure 2A). Similar benefits of apomorphine sublingual film treatment compared with those of placebo were observed at each study visit (figure 2B).

The results of the primary endpoint were supported by each of the prespecified sensitivity analyses. Specifically, the tipping point analysis showed a reversion to a non-significant benefit with the addition (worsening) of 8·5 points in the MDS-UPDRS part 3 score for patients treated with apomorphine sublingual film. However, this degree of worsening was greater than the estimated difference between apomorphine sublingual film and placebo treatment in the primary endpoint analysis, and thus would be implausible. Therefore, the tipping point and other sensitivity analyses supported the robustness of the primary analysis.

The response rate for having a full on response within 30 min at week 12 (key secondary endpoint) was also significantly greater in patients treated with apomorphine sublingual film than in those treated with placebo (table 2). Analysis of home-dosing diaries provided evidence suggesting that patients treated with apomorphine sublingual film reported a full on response at 30 min post-dose more frequently than those treated with placebo (table 2). We also observed benefits of treatment with apomorphine sublingual film for CGI-I, full on response at 15 min, and time to medication effect (on the basis of nominal p values; table 2).

During titration with apomorphine sublingual film, 82 (58%) of 141 patients had at least one treatment-emergent adverse event (table 3). Treatment-emergent adverse events leading to discontinuation during titration occurred in 12 (9%) of 141 patients and included dizziness (four [3%] patients), nausea (three [2%]), somnolence (three [2%]), headache (two [1%]), orthostatic hypotension (two [1%]), and asthenia, blurred vision, head discomfort, hyperhidrosis, hypotension, joint stiffness, musculoskeletal discomfort, pallor, presyncope, suicidal ideation, syncope, upper abdominal pain, and vomiting (one [1%] patient each). During the double-blind maintenance phase, 48 (89%) of 54 patients treated with apomorphine sublingual film had at least one treatment-emergent adverse event compared with 25 (45%) of 55 patients in the placebo group (table 3). During maintenance treatment, treatment-emergent adverse events led to discontinuation of apomorphine sublingual film treatment in 15 (28%) patients and included lip swelling (two [4%] patients), oral mucosal erythema (two [4%]), oropharyngeal swelling (two [4%]), and delusion, disorientation, facial swelling, fall, fatigue,

gingival oedema, irritable bowel syndrome, lip oedema, lip ulceration, mouth oedema, nausea, oral allergy syndrome, oropharyngeal pain, pharyngeal erythema, rhinorrhoea, somnolence, swollen tongue, tongue polyp, urticaria, and vomiting (one [2%] patient each). Treatment-emergent adverse events led to discontinuation of placebo in five (9%) patients during maintenance treatment and included abnormal dreams, confusional state, decreased appetite, disturbance in attention, dyskinesia, erythema, hyperhidrosis, muscle spasms, nightmares, non-infective gingivitis, oral pain, peripheral swelling, and somnolence (in one [2%] patient each). Three patients had serious adverse events during double-blind maintenance treatment; two occurred in patients treated with apomorphine sublingual film (one patient with known cardiac risk factors had a fatal cardiac arrest and another had congestive cardiac failure with hypokalaemia that resolved), and one occurred in a patient treated with placebo (encephalopathy and acute kidney injury that resolved).

Oropharyngeal treatment-emergent adverse events were reported in 17 (31%) of 54 patients receiving apomorphine sublingual film (table 3) and in four (7%) of 55 patients treated with placebo. These events were generally mild to moderate, and no serious or severe events were reported. During the double-blind maintenance phase, oropharyngeal adverse events led to treatment discontinuation in nine (17%) patients treated with apomorphine sublingual film and in one (2%) patient treated with placebo, whereas the remaining eight (15%) patients treated with apomorphine sublingual film and three (5%) treated with placebo who had these events were able to continue the study. Nausea and somnolence were reported more frequently in patients receiving apomorphine sublingual film than in those receiving placebo, but were generally mild and transient. During the double-blind maintenance phase, orthostatic hypotension, hallucinations, and prolongation of the QT interval occurred in one patient each who received apomorphine sublingual film, whereas no patients receiving apomorphine sublingual film had syncope, worsening of dyskinesia, or an impulse control disorder. We found no clinically meaningful differences between treatment groups in vital signs, electrocardiograms, laboratory parameters, QUIP-RS, or C-SSRS. We found no relationship between oropharyngeal and other treatment-emergent adverse events and the dose of apomorphine sublingual film (appendix p 3).

	Apomorphine sublingual film	Placebo (n=55)
TEAEs in >5% of patients in the open-label titration phase		
Any	82 (58%; n=141)	..
Nausea	29 (21%; n=141)	..
Yawning	17 (12%; n=141)	..
Dizziness	16 (11%; n=141)	..
Somnolence	16 (11%; n=141)	..
Headache	11 (8%; n=141)	..
Rhinorrhoea	9 (6%; n=141)	..
Chills	8 (6%; n=141)	..
TEAEs in >5% of patients in the double-blind maintenance phase		
Any	48 (89%; n=54)	25 (45%)
Nausea	15 (28%; n=54)	2 (4%)
Somnolence	7 (13%; n=54)	1 (2%)
Dizziness	5 (9%; n=54)	0
Fatigue	4 (7%; n=54)	0
Oral mucosal erythema	4 (7%; n=54)	2 (4%)
Rhinorrhoea	4 (7%; n=54)	0
Vomiting	4 (7%; n=54)	0
Dry mouth	3 (6%; n=54)	0
Fall	3 (6%; n=54)	1 (2%)
Headache	3 (6%; n=54)	0
Hyperhidrosis	3 (6%; n=54)	2 (4%)
Lacerations (foot or knee)	3 (6%; n=54)	0
TEAEs related to oropharyngeal disorders in ≥2% of patients in the double-blind maintenance phase*		
Oral mucosal erythema	4 (7%; n=54)	2 (4%)
Dry mouth	3 (6%; n=54)	0
Glossodynia	2 (4%; n=54)	0
Lip oedema	2 (4%; n=54)	0
Lip swelling	2 (4%; n=54)	0
Oropharyngeal swelling	2 (4%; n=54)	0
Throat irritation	2 (4%; n=54)	0

Data are n (%) or n (%; N). All TEAEs are listed according to MedDRA (version 19.1). TEAE=treatment-emergent adverse event. MedDRA=Medical Dictionary for Regulatory Activities. *Includes events within MedDRA Standardised MedDRA query oropharyngeal disorders or hypersensitivity.

Table 3: **Summary of adverse events in the safety population**

Discussion

This double-blind, placebo-controlled study showed that treatment with apomorphine sublingual film can rapidly convert an off episode to a full on state in most patients with Parkinson's disease. We observed a significant benefit of apomorphine sublingual film versus placebo in the MDS-UPDRS motor score at 30 min post-dose (primary endpoint), and these results were supported by all sensitivity analyses. Furthermore, the percentage of responders (key secondary endpoint) at the 12-week visit was significantly greater with apomorphine sublingual film than with placebo. Separation from placebo in the MDS-UPDRS motor score was observed as early as 15 min post-dose (first timepoint measured) and persisted up to 90 min (last timepoint measured) at week 12. We also observed a similar pattern of responses to treatment with apomorphine sublingual film versus placebo at each of the previous study visits. Furthermore, the magnitude of separation between apomorphine sublingual film and placebo treatment groups remained constant, suggesting that the effect was maintained over time.

The effectiveness of treatment with apomorphine sublingual film was further supported by multiple secondary endpoints with nominally significant p values, including CGI-I, time to clinical effect, and response in the home

setting based on a dosing diary. Specifically, the time-to-effect analysis suggested that most patients derived clinical benefit within 10–20 min after administration of apomorphine sublingual film, consistent with the significant improvement at 15 min in MDS-UPDRS part 3 score seen in the clinic setting at week 12. Furthermore, results from the home diaries showed that patients treated with apomorphine sublingual film were able to achieve a full on response for most off episodes, compared with those treated with placebo, providing support for the feasibility of self-administration in the home environment. Notably, only 35% of patients treated with apomorphine sublingual film at week 12 showed a full on response at 30 min. This was surprising because nearly 69% of patients achieved a full on response at 30 min during titration at the dose to which they were eventually randomly assigned to. The decrease in responders at 30 min during the double-blind maintenance phase might, in part, have reflected dropouts before the week 12 visit. Nonetheless, the difference was significant compared with the on response rate observed in patients treated with placebo. Additionally, full on responses were reported for nearly 80% of off episodes in the home setting. One explanation for this difference between full on response at 30 min assessed in the clinic and home settings might be that assessments in the clinic were done in a practically defined off state when patients were without dopaminergic therapy for 12 h or longer. Therefore, brain dopamine concentrations were likely to be considerably lower at clinic visits than in the home setting, and the apomorphine sublingual film dose might not have achieved the optimal response during clinic visits.

Treatment-emergent adverse events led to study discontinuation in 28% of patients treated with apomorphine sublingual film and in 9% of those treated with placebo. The most common side-effects leading to discontinuation of apomorphine sublingual film in 17% of patients during the double-blind maintenance phase were mild-to-moderate oropharyngeal adverse events. Nausea, somnolence, and dizziness—well known side-effects of dopamine agonists—were more common with apomorphine sublingual film than with placebo, but were also generally mild, transient, and infrequently led to discontinuation. Notably, treatment with apomorphine sublingual film was not associated with clinically significant worsening of dyskinesia, orthostatic hypotension, impulse control disorders, hallucinations, or unwanted sleep episodes, as have been reported with subcutaneous apomorphine.[14]

Apomorphine sublingual film was designed to deliver apomorphine systemically through absorption from the oral cavity mucosa. Although associated with oropharyngeal events in approximately 30% of patients, this formulation offers an effective alternative for the acute, intermittent management of off episodes, with a relatively long duration of action (up to 90 min; the last timepoint measured). Additionally, unlike levodopa, apomorphine sublingual film does not require co-administration with carbidopa for full effect and, accordingly, this treatment might be particularly useful for early-morning off episodes.

Although the precise mechanism responsible for the development of levodopa-induced off episodes is unknown, it is probably related to the inability of intermittent doses of standard oral levodopa to provide continuous levodopa availability to the brain. Intermittent doses of levodopa cause fluctuating plasma concentrations due to the drug's short half life, variable gastric transport to the jejunum where it is absorbed, and competition for absorption with other large neutral amino acids in the diet.[23–25] Brain dopamine concentrations are normally maintained at a constant level;[26] however, in patients with Parkinson's disease, brain dopamine concentrations are dependent on peripherally available levodopa, where variability in plasma concentrations could result in periods of low brain dopamine concentrations that are insufficient to provide an anti-parkinsonian benefit.[27] Apomorphine sublingual film could provide a reliable on-demand treatment of off episodes that addresses the uncertain bioavailability associated with oral levodopa over time.

Our study has some limitations. We randomly assigned only patients who were responsive to levodopa and achieved a full on response during titration at a tolerable dose, thereby enriching the trial for responders. However, the maintenance phase was double-blind and placebo-controlled, and home-diary data showed that although patients in each treatment group used the study drug to a similar degree in the home setting, the frequency of achieving a full on response strongly favoured treatment with apomorphine sublingual film. Although the treatment effect for off episodes was artificially assessed in the clinic in a practically defined off state, the benefit of apomorphine sublingual film was further substantiated in the home setting, where most off episodes in patients treated with apomorphine sublingual film converted to a full on state at 30 min post-dose compared with those in the placebo group. Furthermore, the higher discontinuation rate in patients treated with apomorphine sublingual film compared with that of those treated with placebo might have affected the efficacy outcomes. However, the efficacy of apomorphine sublingual film was strongly supported by the primary and key secondary endpoints, all sensitivity analyses, and several additional secondary outcomes.

The treatment of off episodes—a common and disabling complication associated with Parkinson's disease—remains a substantial unmet medical need. This double-blind, placebo-controlled study showed that, for most patients who were able to tolerate the treatment, apomorphine sublingual film provides a safe and effective on-demand treatment for off episodes in patients with Parkinson's disease.

Contributors

CWO, PB, KS, and BN did the study concept and design. All authors participated in data acquisition, analysis, or interpretation. PB and KS did the statistical analysis. CWO, PB, KS, and BN drafted the manuscript. All authors critically reviewed the manuscript and approved the final version for submission.

Declaration of interests

CWO is CEO and a shareholder in Clintrex, which provides advisory services to the pharmaceutical industry, and has consulted for Cynapsus Therapeutics and Sunovion. SAF has received honoraria from Acadia, Acorda, Adamas, Biogen, Bracket Global, CereSpir, Lundbeck, Neurocrine, Prexton Therapeutics, Sunovion, and Teva; grant support from CHDI Foundation, Ipsen, Eli Lilly, Jazz Pharmaceuticals, Medtronics, Michael J Fox Foundation, National Institutes of Health, Sunovion, Teva, US WorldMeds, Vaccinex, and Voyager; and royalties from Blackwell Futura for textbooks, Demos, and UpToDate. HAS has received grants from Biogen, Dong-A, Intec Pharma, Sunovion, and US WorldMeds and personal fees from AbbVie and Sunovion. SI has received honoraria for continuing medical education, consultancy services, research grants, or promotional speaking from AbbVie, Acadia, Acorda, Adamas, Addex, Allergan, Amarantus, Axovant, Benevolent, Biogen, Britannia, Cerecor, Eli Lilly, Enterin, GE Healthcare, Global Kinetics, Impax, Intec Pharma, Ipsen, Jazz, Kyowa, Lundbeck, Michael J Fox Foundation, Neurocrine, NeuroDerm, Parkinson Study Group, Pharma Two B, Roche, Sanofi, Sunovion, Teva, Theravance, UCB, US WorldMeds, and Zambon. RAH has received consulting fees from AbbVie, Academy for Continued Healthcare Learning, Acadia, Acorda, Adamas, ApoPharma, AstraZeneca, Back Bay Life Science, Biotie Therapies, Bracket, Cerecor, ClearView Healthcare Partners, ClinicalMind Medical and Therapeutic Communications, CNS Ratings, Cowen and Company, Cynapsus Therapeutics, DDB Health, Decision Resources Group, Eli Lilly, eResearch Technology, Expert Connect, Extera Partners, GE Healthcare, Health Advances, HealthLogix, Health and Wellness Partners, Huron Consulting Group, Impax, Impel Neuropharma, Intec Pharma, Jazz, Kashiv Pharma, Kyowa, LCN Consulting, LifeMax, Life Sciences, Lundbeck, The Lockwood Group, MEDACorp, Medscape, Medtronic, Michael J Fox Foundation, Mitsubishi Tanabe Pharmaceuticals, Movement Disorder Society, National Institutes of Health, Neurocea, Neurocrine Biosciences, Neuroderm, Neuropore Therapies, Orbes Medical Group, Outcomes Insights, Parkinson Study Group, Peerview Press, Pennside Partners, Pfizer, Pharma Two B, Phase Five Communications, Prescott Medical Group, Prexton Therapeutics, Prilenia Development, Projects in Knowledge, Putnam Associates, Quintiles, RMEI Medical Education for Better Outcomes, SAI Med Partners, Sarepta Therapeutics, Schlesinger Associates, Scion Neurostim, Seagrove Partners, Seelos, Slingshot Insights, Sun Pharma, Sunovion, Teva, US WorldMeds, Vista Research, WebMD, Windrose Consulting Group; research support from AbbVie, Acorda, AstraZeneca, Axovant Sciences, Biogen, Cavion, Dart NeuroScience, Enterin, F Hoffman-La Roche, Impax, Intec, Jazz, Lundbeck, Michael J Fox Foundation, NeuroDerm, Prexton Therapeutics, Revance Therapeutics, and Sunovion; and grant support from the Parkinson's Foundation. AJE has received grant support from Great Lakes Neurotechnologies, Michael J Fox Foundation, and the National Institutes of Health; personal compensation as a consultant or scientific advisory board member for AbbVie, Acadia, Acorda, Adamas, Impax, Lundbeck, Neuroderm, Osmotica Pharmaceutical, Sunovion, Teva, and US WorldMeds; publishing royalties from Cambridge University Press, Lippincott Williams & Wilkins, and Springer; and honoraria from AbbVie, Acadia, American Academy of Neurology, Lundbeck, Movement Disorders Society, Sunovion, UCB, and US WorldMeds. RP has received personal fees for consulting or speaker services from Abbott, AbbVie, Acadia, Acorda, Adamas, Cala Health, Global Kinetics, Lundbeck, Neurocrine, PhotoPharmics, Prilenia, Sunovion, Teva Neuroscience, and US WorldMeds; and grant support from Abbott, AbbVie, Acorda, Biogen, Boston Scientific, Cala Health, Cavion, Cynapsus Therapeutics, Eli Lilly, Intec, Jazz, Kyowa, National Institutes of Health—National Institute of Neurological Disorders and Stroke, National Parkinson's Foundation, Parkinson's Study Group, Roche, Sunovion, Theranexus, Theravance, US WorldMeds, and Voyager. ML is a biostatistical advisor for Clintrex and has consulted specifically for Acorda, Avadel, Cynapsus Therapeutics, Dart Neuroscience, Intec, NeuroDerm, Novartis, Pharma Two B, PhotoPharmics, Prilenia Therapeutics, Raptor Pharmaceuticals, Remedy Pharmaceuticals, Roche, Santhera Pharmaceuticals, Serina Therapeutics, Sunovion, Swedish Orphan Biovitrum, Synagile Corporation, Ultragenyx, Voyager Therapeutics, and vTv Therapeutics. PB, KS, BN, and DB are employees of Sunovion.

Data sharing

Access to de-identified participant data will be provided after a research proposal is submitted online and receives approval from the Independent Review Panel and after a data sharing agreement is in place. Access will be provided for an initial period of 12 months, but an extension can be granted, when justified, for up to an additional 12 months.

For the **online submission of research proposals** see http://clinicalstudydatarequest.com

Acknowledgments

Sunovion (Marlborough, MA, USA), through its wholly owned subsidiary Sunovion CNS Development Canada, acquired Cynapsus Therapeutics and its product candidate, APL-130277, on Oct 21, 2016. The study was funded and done by Cynapsus Therapeutics and Sunovion. The authors would like to thank Karl Kieburtz, MD (Clintrex, Sarasota, FL, USA; and University of Rochester, Rochester, NY, USA), for his contributions to this work. Copyediting and graphics services were provided by The Lockwood Group (Stamford, CT, USA) and funded by Sunovion.

References

1 Marras C, Beck JC, Bower JH, et al. Prevalence of Parkinson's disease across North America. *NPJ Parkinsons Dis* 2018; **4:** 21.
2 Ahlskog JE, Muenter MD. Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature. *Mov Disord* 2001; **16:** 448–58.
3 Hely MA, Morris JG, Reid WG, Trafficante R. Sydney Multicenter Study of Parkinson's disease: non-L-dopa-responsive problems dominate at 15 years. *Mov Disord* 2005; **20:** 190–99.
4 Olanow CW, Kieburtz K, Rascol O, et al. Factors predictive of the development of levodopa-induced dyskinesia and wearing-off in Parkinson's disease. *Mov Disord* 2013; **28:** 1064–71.
5 Hung SW, Adeli GM, Arenovich T, Fox SH, Lang AE. Patient perception of dyskinesia in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2010; **81:** 1112–15.
6 Chou KL, Stacy M, Simuni T, et al. The spectrum of "off" in Parkinson's disease: what have we learned over 40 years? *Parkinsonism Relat Disord* 2018; **51:** 9–16.
7 Chapuis S, Ouchchane L, Metz O, Gerbaud L, Durif F. Impact of the motor complications of Parkinson's disease on the quality of life. *Mov Disord* 2005; **20:** 224–30.
8 Martinez-Martin P, Rodriguez-Blazquez C, Kurtis MM, Chaudhuri KR, NMSS Validation Group. The impact of non-motor symptoms on health-related quality of life of patients with Parkinson's disease. *Mov Disord* 2011; **26:** 399–406.
9 van der Velden RMJ, Broen MPG, Kuijf ML, Leentjens AFG. Frequency of mood and anxiety fluctuations in Parkinson's disease patients with motor fluctuations: a systematic review. *Mov Disord* 2018; **33:** 1521–27.
10 Ray Chaudhuri K, Poewe W, Brooks D. Motor and nonmotor complications of levodopa: phenomenology, risk factors, and imaging features. *Mov Disord* 2018; **33:** 909–19.
11 Merims D, Djaldetti R, Melamed E. Waiting for ON: a major problem in patients with Parkinson disease and ON/OFF motor fluctuations. *Clin Neuropharmacol* 2003; **26:** 196–98.
12 Olanow CW, Stocchi F. Levodopa: a new look at an old friend. *Mov Disord* 2018; **33:** 859–66.
13 Boyle A, Ondo W. Role of apomorphine in the treatment of Parkinson's disease. *CNS Drugs* 2015; **29:** 83–89.
14 Dewey RB Jr, Hutton JT, LeWitt PA, Factor SA. A randomized, double-blind, placebo-controlled trial of subcutaneously injected apomorphine for parkinsonian off-state events. *Arch Neurol* 2001; **58:** 1385–92.
15 Hughes AJ, Bishop S, Kleedorfer B, et al. Subcutaneous apomorphine in Parkinson's disease: response to chronic administration for up to five years. *Mov Disord* 1993; **8:** 165–70.
16 Manson AJ, Turner K, Lees AJ. Apomorphine monotherapy in the treatment of refractory motor complications of Parkinson's disease: long-term follow-up study of 64 patients. *Mov Disord* 2002; **17:** 1235–41.
17 Unti E, Ceravolo R, Bonuccelli U. Apomorphine hydrochloride for the treatment of Parkinson's disease. *Expert Rev Neurother* 2015; **15:** 723–32.
18 Pahwa R, Koller WC, Trosch RM, Sherry JH, APO303 Study Investigators. Subcutaneous apomorphine in patients with advanced Parkinson's disease: a dose-escalation study with randomized, double-blind, placebo-controlled crossover evaluation of a single dose. *J Neurol Sci* 2007; **258:** 137–43.

19 Bilbault T, Taylor S, Walker R, Grundy SL, Pappert EJ, Agro A. Buccal mucosal irritation studies of sublingual apomorphine film (APL-130277) in Syrian golden hamsters. *Ther Deliv* 2016; **7:** 611–18.

20 Hauser RA, Olanow CW, Dzyngel B, et al. Sublingual apomorphine (APL-130277) for the acute conversion of OFF to ON in Parkinson's disease. *Mov Disord* 2016; **31:** 1366–72.

21 Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry* 1992; **55:** 181–84.

22 Goetz CG, Tilley BC, Shaftman SR, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. *Mov Disord* 2008; **23:** 2129–70.

23 Muenter MD, Tyce GM. L-dopa therapy of Parkinson's disease: plasma L-dopa concentration, therapeutic response, and side effects. *Mayo Clin Proc* 1971; **46:** 231–39.

24 Nutt JG, Fellman JH. Pharmacokinetics of levodopa. *Clin Neuropharmacol* 1984; **7:** 35–49.

25 Olanow CW, Obeso JA, Stocchi F. Continuous dopamine-receptor treatment of Parkinson's disease: scientific rationale and clinical implications. *Lancet Neurol* 2006; **5:** 677–87.

26 Abercrombie ED, Bonatz AE, Zigmond MJ. Effects of L-dopa on extracellular dopamine in striatum of normal and 6-hydroxydopamine-treated rats. *Brain Res* 1990; **525:** 36–44.

27 Stocchi F, Vacca L, Ruggieri S, Olanow CW. Intermittent vs continuous levodopa administration in patients with advanced Parkinson disease: a clinical and pharmacokinetic study. *Arch Neurol* 2005; **62:** 905–10.

28 LeWitt PA, Hauser RA, Pahwa R, et al. Safety and efficacy of CVT-301 (levodopa inhalation powder) on motor function during off periods in patients with Parkinson's disease: a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet Neurol* 2019; **18:** 145–54.