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CADTH COMMON DRUG REVIEW

Clinical Review Report

Apomorphine (Movapo)

(Paladin Labs Inc.)

Indication: The acute, intermittent treatment of hypomobility “off” episodes (“end-of-dose wearing off” and unpredictable “on/off” episodes) in patients with advanced Parkinson’s disease

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Abbreviations

AE	adverse event
ANCOVA	analysis of covariance
ANOVA	analysis of variance
CDR	CADTH Common Drug Review
CGI-I	Clinical Global Impression of Improvement
DBP	diastolic blood pressure
DRS	Dyskinesia Rating Scale
H&Y	Hoehn and Yahr
HTT	hand-tapping test
ICC	intraclass correlation coefficient
ITT	intention-to-treat
MCID	minimal clinically important difference
PC	Parkinson Canada
PD	Parkinson's disease
PGI-I	Patient Global Impression of Improvement
PP	per-protocol
PSBC	Parkinson Society British Columbia
SAE	serious adverse event
SBP	systolic blood pressure
TED	therapeutically equivalent dose
UPDRS	Unified Parkinson's Disease Rating Scale
WDAE	withdrawal due to adverse event
WSST	Webster step-seconds test

Drug	Apomorphine hydrochloride (MOVAPO, pre-filled pens, 10mg/mL, 3 mL, subcutaneous injection)
Indication	MOVAPO (apomorphine hydrochloride 10mg/mL) is indicated for: The acute, intermittent treatment of hypomobility “off” episodes (“end-of-dose wearing off” and unpredictable “on/off” episodes) in patients with advanced Parkinson’s disease.
Reimbursement Request	As per indication
Manufacturer	Paladin Labs Inc.

Executive Summary

Introduction

Parkinson’s disease (PD) is a progressive neurodegenerative disease featuring impaired motor function resulting from continuous degeneration of dopaminergic neurons. Patients suffer from characteristic resting tremor, rigidity, bradykinesia, and postural instability, leading to a loss of control of voluntary movement. Surveys from 2010 to 2012 indicate an estimated 67,500 people in Canada have a diagnosis of PD.

Apomorphine hydrochloride is a potent post-synaptic dopamine agonist. The Health Canada–approved indication for apomorphine is for treatment of acute, intermittent hypomobility “off” episodes (“end-of-dose wearing off” and unpredictable “on/off”) in patients with advanced PD. The information included in the product monograph indicates that apomorphine is available in 2 mL ampoules or 3 mL pre-filled, disposable, multi-dose pens at a strength of 10 mg/mL; however, the manufacturer of apomorphine indicated that the 2 mL ampoules will never be marketed and distributed in Canada. The recommended range is 0.2 mL (2 mg) to 0.6 mL (6 mg) per dose, to be administered subcutaneously as an adjunct to regular oral anti-PD medications.

The objective of this review was to perform a systematic review of the beneficial and harmful effects of apomorphine (Movapo) as an adjunct to oral anti-PD medications to treat patients with advanced PD.

Results and Interpretation

Included Studies

The evidence for this review as it pertains to the use of apomorphine for the treatment of intermittent “off” episodes (“end-of-dose wearing off” and unpredictable “on/off”) as an adjunct to anti-PD medications in patients with advanced PD was drawn from three double-blind, multi-centre, placebo-controlled randomized controlled trials. All patients received apomorphine via subcutaneous injection, were on an optimized oral anti-PD medication regimen, and had late-stage PD.

APO 202 (N = 29) was a phase II, parallel-group trial designed to assess the therapeutic efficacy and safety of apomorphine. The trial consisted of an in-patient dose-titration phase

followed by an outpatient phase of four weeks. During the dose-titration phase, patients' response to a dopaminergic challenge was assessed followed by up-titration of apomorphine dose until a therapeutically equivalent dose (TED, defined as ≥ 90% of the motor response elicited during dopaminergic challenge) was achieved (mean dose, 5.4 mg/dose; range, 2 mg to 10 mg) to treat induced "off" episodes. During the outpatient phase, patients self-administered TED of apomorphine as a rescue medication to reverse spontaneous "off" episodes (mean dose, 5.8 mg/dose; ≤ 5 doses/day).

APO 301 (N = 17) was a phase III, crossover trial where patients on apomorphine treatment for at least three months (mean duration, 2.5 years) were included to evaluate the continued efficacy of their usual dose of apomorphine to treat "off" episodes. Efficacy was evaluated using a single, alternate dose of apomorphine (mean dose, 3.9 mg/bolus) or placebo randomized to be given on two separate days.

APO 302 (N = 62) was a phase III, parallel-group, single-dose trial which was part of a large open-label safety trial (APO 401). Patients in this trial were also exposed to apomorphine for at least three months (mean duration 14.5 months; 3.8 mg/injection). The design was similar to that of APO 301, except for the absence of crossover of treatment and the inclusion of four dose groups. Patients were randomized to receive one of the following in 2:2:1:1 ratio: patient's usual dose of apomorphine (mean dose, 4.6 mg/dose), patient's usual dose of apomorphine plus 0.2 mL (mean dose, 5.8 mg/dose), placebo volume-matched with patient's usual dose of apomorphine, and placebo volume-matched with patient's usual dose of apomorphine plus 0.2 mL.

The primary efficacy outcome in all three trials was change in Unified Parkinson's Disease Rating Scale (UPDRS) Part III motor score from pre-dose "off" state (induced or spontaneous "off") to approximately 20 minutes post-dose. A number of secondary outcomes were measured, including different time points of UPDRS-III, hand-tapping test (HTT) score, Dyskinesia Rating Scale (DRS) score, Webster step-seconds test (WSST) score, time to response from injection to clinically or self-determined "on" state, frequency and duration of "off" events, and number of injections that aborted "off" events. In addition, any serious or non-serious adverse events (AEs), withdrawal due to adverse events (WDAEs), and notable harms (e.g., dyskinesia, orthostatic hypotension) were recorded.

A major limitation common to all included trials was the potential unblinding of patient and outcome assessors to treatment allocation. Since the change in motor function following apomorphine dosing was easily recognizable, the extent to which blinding was maintained throughout the duration of the trials is uncertain. In particular, patients in the APO 301 and APO 302 trials were experienced with the effects of apomorphine during "off" episodes before study enrolment. Patients in the APO 202 trial may have become familiar with treatment-elicited response during the in-patient phase and surmised their treatment during the outpatient phase. This may have affected the results, particularly if the outcomes were subjective and, hence, prone to reporting bias. The clinical expert consulted for this review indicated an element of subjectivity present in assessment of outcomes based on scales, especially within closely separated scale elements. UPDRS is a commonly used and validated tool; however, the use and psychometric properties of HTT, WSST, and DRS are not as well-characterized. None of the trials conducted statistical analyses after adjusting for multiple comparisons, and results from all analyses other than the primary efficacy outcome should be interpreted with consideration of the risk of type I error. Finally, the trial durations may not have been long enough for patients to develop treatment-emergent AEs. The

results from two long-term safety trials, APO 303 and APO 401, are summarized in Appendix 6.

Results from a systematic review pertaining to the safety and efficacy of intermittent, subcutaneous administration of apomorphine in patients with PD are summarized in Appendix 7. Among many other limitations, this was a systematic review without a meta-analysis, which mostly included studies that were not randomized or controlled, and that had unclear methodology for unweighted pooled effect estimates. A total of eight trials and 195 patients were included, and the mean dose ranged from 1.9 mg to 5.4 mg per injection.

Efficacy

Overall, there was a clinically and statistically significant improvement in mean UPDRS-III motor score in favour of apomorphine treatment across all trials. The percentage decreases in mean UPDRS-III motor score at or around 20 minutes following apomorphine treatment were 61.7%, 47.4%, and 58.7% in APO 202, APO 301, and APO 302, respectively, and the scores were statistically significantly different compared with placebo.

The secondary outcomes discussed next all showed an improvement in favour of apomorphine; however, due to a lack of adjustment for multiplicity, the results could not be interpreted with reference to statistical significance. The change in UPDRS-III score was measured at different time points in APO 301 and APO 302, and numerical decreases in motor score of about 36% and 49%, respectively, were found at 10 minutes post-dose compared with pre-dose values. The per cent decreases at 60 minutes and 90 minutes post-dose compared with pre-dose values were not numerically as high as the earlier time points, but were still more than 30% and 13% in APO 301 and APO 302, respectively. In the APO 303 trial discussed in the Appendix 6, similar results were found for patients receiving apomorphine during the crossover double-blind phase, where apomorphine-treated patients experienced a greater reduction in UPDRS-III score compared with placebo at 20 minutes (−11.2 versus −2.8), 40 minutes (−13.5 versus −3.0), and 90 minutes (−5.1 versus −1.6) post-dose, all of which were statistically significant.

The severity of dyskinesia was higher in the apomorphine-treated group across all trials and was mild to moderate in intensity as measured using DRS. HTT score was assessed only during the in-patient phase of the APO 202 trial, and an 88% increase from the pre-dose mean score was registered in the apomorphine-treated patients compared with a −4% change in the placebo group. The median WSST score from pre-dose values decreased by about 65% in the APO 202 trial without any concomitant change in the placebo group. In the APO 302 trial, a gradual decrease in median WSST score at all time points up to 40 minutes was found, and the decrease was numerically greater than that of the placebo group. In the APO 202 trial, there was a mean decrease of 1.7 hours in “off” episodes in the apomorphine group from baseline, without any such reduction in the placebo group. In addition, the mean time to response following apomorphine injection decreased by half compared with placebo (22.1 versus 44.8 minutes). The mean time to response was numerically lower following apomorphine injection in the two single-dose trials compared with placebo (15 minutes versus 60 minutes and 5 minutes versus 7.5 minutes in APO 301 and APO 302, respectively). In APO 202 the proportion of “off” events that were aborted following apomorphine treatment was 95.2%, versus 23.1% with placebo. In the systematic review discussed in Appendix 7, the mean reduction in daily “off” state for patients receiving

apomorphine ranged from 33% to 58% compared with either placebo or pre-apomorphine values.

Harms

Overall, the AEs found in the trials were mild to moderate in intensity and were known side effects of apomorphine treatment, including injection site reactions, yawning, dyskinesia, fatigue, somnolence, dizziness, nausea/vomiting, and falls. The frequency of AEs was highest in APO 202 with ≥ 85% reporting an AE, followed by patients in the single-dose APO 302 (> 40%) and APO 301 trials (> 17%). Only one serious adverse event (SAE) and three non-serious but significant AEs were reported in APO 202, all of them involving chest pain, pressure, or angina symptoms. Two patients in the APO 202 trial discontinued treatment due to chest pain (placebo) and nausea (apomorphine), neither of which were SAEs. Three patients in total receiving placebo discontinued treatment in the APO 301 (n = 1) and APO 302 (n = 2) trials due to lack of treatment effect. Among notable AEs, orthostatic hypotension was found in patients receiving apomorphine in both phase III trials. A total of 6% (0% in the placebo group) and 31% (12% in the placebo group) of patients in the APO 301 trial receiving apomorphine reported decreases in systolic blood pressure (SBP) and diastolic blood pressure (DBP), respectively, that fell within the clinically defined orthostatic hypotension range; in APO 302, more than 34% of patients in the apomorphine group and 48% of patients in the placebo group met this definition. However, only three cases occurred exclusively post-dose in APO 302, and information was not provided in APO 301. The frequency of dyskinesia, a known side effect of apomorphine, was increased in all three trials; however, this did not prevent the patients from performing motor tasks.

In the two long-term safety trials, APO 303 and APO 401, the vast majority of the patients reported at least one AE (> 90%), and the AEs mostly included the same known side effects of apomorphine listed above. The study discontinuation rates in APO 303 and APO 401 were 41% and 78%, respectively, and approximately one-third of the withdrawals were due to AEs (30% and 34%, respectively). In the APO 303 trial, only four SAEs were recorded, one of which, syncope and sinus arrest, was related to apomorphine treatment. On the other hand, 199 patients in the APO 401 trial reported occurrence of SAEs, of which 27 cases in 19 patients were considered treatment-related. These SAEs involved various cardiovascular (syncope, postural hypotension, atrial flutter, atrial fibrillation, congestive cardiac failure, cardiac sinus arrest), musculoskeletal (bradycardia, musculoskeletal pain, falls), neurological (confusion, depressed level of consciousness, dysarthria, hallucinations, lethargy, mood disorder), and psychological symptoms (psychosis, personality change). In the APO 303 trial, sitting and standing SBP and DBP decreased with increasing apomorphine dose at 20 and 40 minutes post-dose; and orthostatic hypotension was seen in no more than 20% of all patients. However, symptomatic hypotension (dizziness and lightheadedness) was more common in the apomorphine group at 20 minutes (17.6%) and 40 minutes (11.8%) post-dose compared with placebo (7.8% and 2.0% at 20 and 40 minutes, respectively). Patients in the APO 401 trial reported orthostatic hypotension more frequently pre-apomorphine and post-apomorphine dosing in both in-patient (14.0% versus 23.4%, respectively) and outpatient (23.3% versus 27.5%, respectively) settings; and 87% of the orthostatic hypotension cases were asymptomatic. A total of 78% patients reported dyskinesia. Overall, no additional AEs, other than those reported in the short-term safety trials, were identified in the long-term safety trials.

Potential Place in Therapy[1]

Since its introduction into clinical practice almost 50 years ago, levodopa remains the most effective treatment for the motor manifestations of PD. However, levodopa is only a symptomatic treatment. It does not slow the underlying neurodegenerative process in PD, and the number of functioning nigrostriatal pathway neurons continues to decline. As the number of remaining functioning nigrostriatal neurons falls, the midbrain's ability to convert levodopa to dopamine and thereby stimulate the striatum becomes increasingly impaired. Clinically, this decline in the nigrostriatal population is experienced by patients as a gradual transition from the initial months or years in which levodopa produces a sustained, continuous improvement in motor function to a state in which individual doses of levodopa produce increasingly shorter periods of improvement, which wear off quickly. As PD advances, more and more the patient alternates between "on" periods, when they are mobile, and "off" periods, when they are immobile. Generally the fluctuation between the "on" and "off" states can be related to when individual doses of levodopa are administered. To some extent, this fluctuation can be minimized by spacing levodopa doses closer together and using additional drugs such as sustained-release levodopa preparations, drugs that inhibit the metabolism of levodopa, or direct dopamine agonists (the latter generally have a longer duration of action than levodopa but are also unfortunately generally less effective). Although patients can learn to adapt to these fluctuations to some extent, the fluctuations can be unpredictable, severe, and have a major impact on their ability to carry out tasks of daily living.

Apomorphine has long been known to be an effective and rapidly acting dopamine agonist. Its use has been limited because of its poor oral bioavailability. However, when administered by injection in response to an "off" state, apomorphine is able to act rapidly and offers patients the possibility of a quick (within a half-hour) improvement in mobility, although the benefit rarely lasts more than an hour. Injectable apomorphine is thus likely to find a useful niche as an additional therapy for PD patients who experience prominent fluctuations between "on" and "off" states during the day (whether clearly related to the timing of levodopa doses or occurring unpredictably), as well as for those who are disabled by impaired mobility upon awakening in the morning (i.e., before they have taken their first morning dose of levodopa).

The patients most likely to find injectable apomorphine helpful are those with moderately advanced PD (disabled, but still ambulatory and at least semi-independent). Identification of such patients would be part of routine neurological follow-up and would not require any new or specific diagnostic testing.

Conclusions

In this CADTH Common Drug Review (CDR) systematic review, three randomized, double-blind, placebo-controlled trials were included to assess the therapeutic efficacy and safety of intermittent, subcutaneous apomorphine as an adjunct therapy to standard anti-PD medications to treat "off" episodes (e.g., "end-of-dose wearing off" or unpredictable "off") in late-stage PD patients (Hoehn and Yahr stage 2 to 4).

Overall, a statistically significant improvement in motor function based on the primary efficacy parameter, UPDRS-III motor score from baseline to 20 minutes post-dose, was found with apomorphine treatment compared with placebo in all studies. Changes in motor

[1] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

function were measured using a number of additional secondary outcome variables (e.g., HTT, WSST, DRS), and all showed numerical improvements compared with baseline or pre-dose "on" values. However, due to the lack of control for multiplicity in any of the trials, results from these outcomes could not be interpreted with reference to statistical or clinical significance. Patients treated with apomorphine reported a decrease in total daily "off" hours, successfully aborting most "off" episodes, and the time to onset of symptom relief was shorter than that in the placebo group; however, these outcomes were also not controlled for multiple statistical testing. In terms of AEs, the short-term studies confirmed the side effects that are commonly associated with apomorphine treatment, including but not limited to dyskinesia, orthostatic hypotension, falls, somnolence, dizziness, yawning, hallucination, and nausea/vomiting. SAEs were not frequently reported with apomorphine treatment, and the AEs were mostly mild to moderate in severity. The long-term studies found similar AEs as reported in the short-term studies, but long-term efficacy could not be assessed.

Table 1: Summary of Results

End Point	APO 202		APO 301		APO 302[a]	
	APO (N = 20)	PLB (N = 9)	APO (N = 17)	PLB (N = 17)	Pooled APO (N = 35)	Pooled PLB (N = 27)
UPDRS Motor Score, Mean (SE)						
Pre-dose "off" state	39.6 (1.9)	36.3 (2.3)	41.3 (2.5)	40.1(2.2)	42.0 (1. 8)	40.6 (3 .4)
20 minutes post-dose	15.8 (2.4)	36.2 (3.1)	21.3 (3.5)	37.1 (2.3)	17.8 (1. 9)	33.3 (4 .4)
Change from pre-dose	−23.8	−0.1	−21.3 (3.5)	−3.0 (2.2)	−24.2 (1. 7)	−7.4 (1. 8)
P value[b]	< 0.0001				< 0.0001	
Difference in score change between APO and PLB	NR		NR		−16.9 (2.5)	
P value[c]	NR		NR		< 0.0001	
% change from pre-dose	−61.7	−1.0	−47.4	−5.9	−58.7 (3. 8)	−24.1 (5. 6)
P value[d]	< 0.0001		< 0.0001		< 0.0001	
Daily Total Time in "Off" State (Hour), Mean						
N	18	8	17	17	35	27
Baseline	5.8	6.5	NR	NR	NR	NR
Post-baseline	4.1	6.5	NR	NR	NR	NR
Change from baseline, mean	−1.7	0.0	NR	NR	NR	NR
P value[b]	0.08		NR	NR	NR	NR
Change from baseline, median	−2.0	0.0	NR	NR	NR	NR
P value[b]	0.01		NR	NR	NR	NR
Hand-Tapping Score, Mean (SE)						
N	19	9	17	17	35	27
"Off"-state score	265.2 (22.1)	255.0 (15.9)	NR	NR	NR	NR
Change from pre-dose	108.7	−11.9	NR	NR	NR	NR
P value[b]	0.0008		NR	NR	NR	NR

End Point	APO 202		APO 301		APO 302[a]	
	APO (N = 20)	PLB (N = 9)	APO (N = 17)	PLB (N = 17)	Pooled APO (N = 35)	Pooled PLB (N = 27)
% change from pre-dose	87.8	−4.11	NR	NR	NR	NR
P value[d]	0.1		NR	NR	NR	NR
Webster Step-Seconds Score, Median (Min, Max)						
N	20	9	17	17	35	27
"Off"-state score	552 (9,820)[e]	273 (9,734)[e]	NR	NR	683	760
"On"-state score at 20 minutes post-dose	128 (97)[e]	323 (9,804)[e]			143	378
Change from pre-dose	−402 (9,701)	0 (29)	NR	NR	−462.5 (−9,927, 8)	−39 (−9,819, 9,299)
P value[b]	< 0.001		NR	NR	< 0.0001	
% change from pre-dose	−65 (65)	0 (14)	NR	NR	NR	NR
P value[d]	NR		NR	NR	NR	
Dyskinesia Rating Scale Score, Median (Min, Max)						
N	20	9	17	17	35	27
"Off"-state score/pre-dose score	0	0	NR	NR	0	0
"On"-state score	1 (1.5)[e]	0	NR	NR	NR	NR
Change from pre-dose	1 (1.5)[e]	0	NR	NR	NR	NR
P value[b]	0.001		NR		NR	
10 minutes post-dose	NR	NR	0 (0, 2)	0 (−3, 0)	0	0
P value[b]	NR		0.02		NR	
% change from pre-dose	NR	NR	NR	NR	0.0 (−1, 2)	0.0 (−1, 2)
P value[d]	NR		NR		0.002	
20 minutes post-dose	NR	NR	1 (−3, 3)	0 (0, 0)	1	0
P value[b]	NR		0.05		NR	
% change from pre-dose	NR	NR	NR	NR	0.0 (−1, 2)	0.0 (−1, 0)
P value[d]	NR		NR		< 0.0001	
60 or 90 minutes post-dose	NR	NR	0 (−3, 3)	0 (−3, 0)	0	0
P value[b]	NR		0.11		NR	
% change from pre-dose	NR	NR	NR	NR	0.0 (0, 1)	0.0 (−1, 2)
P value[d]	NR		NR		0.25	
Withdrawals						
n (%)	3 (15)	0	0	1 (11)	0	2 (15.4)
SAEs						
n (%)	0	1 (11.1)	0	0	0	0
WDAEs						
n (%)	2 (10)	0	0	0	0	0
Dyskinesia						
n (%)	7 (35)	1 (11)	0 (0)	0 (0)	1 (2.9)	1 (3.7)

End Point	APO 202		APO 301		APO 302[a]	
	APO (N = 20)	PLB (N = 9)	APO (N = 17)	PLB (N = 17)	Pooled APO (N = 35)	Pooled PLB (N = 27)
Orthostatic Hypotension						
SBP decrease ≥ 20 mm Hg (%)	NR	NR	6	0	12	13
DBP decrease ≥ 10 mm Hg (%)	NR	NR	31	12		

ANCOVA = analysis of covariance; APO = apomorphine; CSR = Clinical Study Report; DBP = diastolic blood pressure; max = maximum; min = minimum; NR = not reported; PLB = placebo; SAE = serious adverse event; SBP = systolic blood pressure; SE = standard error; UPDRS = Unified Parkinson's Disease Rating Scale; WDAE = withdrawal due to adverse event.

Notes: *P* values for the raw score change and % change for UPDRS motor exam score, hand-tapping test score and Webster step-seconds test score were derived from an ANCOVA; *P* values for the median change for the Dyskinesia Rating Scale were derived from the Wilcoxon rank sum test.

Other than *P* values for the UPDRS-III score, all *P* values should be interpreted with caution since they were not adjusted for type I error.

Patients in the APO and PLB groups were pooled for ease of reporting and because no statistically significant difference was found between the two PLB groups based on the primary efficacy analysis.

[a] Pooled APO includes patients who received APO in their typically effective dose or typically effective dose + 0.2 mL; pooled PLB includes patients who received PLB volume-matched to APO or PLB + 0.2 mL.

[b] *P* value comparing raw score change from pre-dose or baseline between APO and PLB groups.

[c] *P* value comparing difference in change between APO and PLB groups.

[d] *P* value comparing per cent change from pre-dose between APO and PLB groups.

[e] Median (Q3 to Q1), indicating difference between 75th and 25th percentile.

Source: Study 202 CSR,[1] Study 301 CSR,[2] Study 302 CSR,[3] Health Canada Reviewers Report.[4]

Introduction

Disease Prevalence and Incidence

Parkinson's disease (PD) is a progressive, neurodegenerative disease that involves impaired motor functions and generally affects individuals greater than 50 years of age. Canadian survey data from 2010 to 2012 yielded estimates of prevalence rates for diagnosed PD of 0.2% in the household population and 4.9% in residents of long-term care facilities.[5] It was estimated that there were 55,000 people in the household population and 12,500 in long-term care facilities with a PD diagnosis in Canada.[5] Of those with a PD diagnosis, 79% and 97% were at least 65 years of age in the household population and in long-term care facilities, respectively.[5] The predisposition of PD increases with age, as 85% of diagnosed cases are in people older than 65, and the incidence and severity increase with age. PD is relatively more common in males and Caucasians.[4,6]

The characteristic features of PD include resting tremor, rigidity, bradykinesia, and postural instability leading to loss of control of voluntary movement. The impairment in motor functions may worsen over time, resulting in debilitating disability by 10 to 15 years after onset. The underlying cause of motor symptoms is a combination of chronic degeneration of the dopaminergic neurons in the nigrostriatal region of the brain and depletion of dopamine. PD is also associated with non-motor symptoms, such as gastrointestinal symptoms, neuropsychiatric symptoms, sleep disturbances, urinary dysfunction, pain, and impulse control disorders.[4,6]

Patients in advanced-stage PD often present with dyskinesia and motor fluctuations, which may manifest as unpredictable "off" times (immobility/hypomobility), unpredictable "on/off" fluctuations, and "end-of-dose wearing off" episodes. "Off" times can involve problems in breathing and swallowing in addition to rigidity, dystonia, tremor, and freezing. Patients frequently report an increase in daily "off" time and concomitant shortening of "on" time as the disease progresses. Patient and caregiver quality of life is therefore severely affected, as maintaining a social life and performing daily activities, work, household chores, and recreational activities become difficult or impossible and require significant planning and dependence on caregivers.

Standards of Therapy

The therapies for idiopathic PD vary by the severity of the symptoms and the disease as well as patients' characteristics.[7] Treatments for motor symptoms can be broadly categorized as pharmacologic and surgical therapy. Pharmacologic treatments can be further divided into neuroprotective and symptomatic therapies based on their mode of action.[8] In practice, most therapies for PD are pharmacologic in nature, are administered orally, and aim to treat motor symptoms and the underlying cause of depleting dopamine levels in the brain.

A number of dopaminergic anti-PD medications are marketed worldwide and in Canada. Levodopa, a precursor of dopamine, is the first-line treatment due to its effectiveness in minimizing motor-related symptoms of PD, including tremor, rigidity, and bradykinesia, by restoring dopamine deficiency at the nigrostriatal region in the brain.[4,7,8] The Canadian Guidelines on Parkinson's Disease[7] recommend that oral levodopa be given in combination with any of the following based on PD stage and tolerability: fixed combination with dopa-decarboxylase inhibitors (carbidopa or benserazide), monoamine oxidase type B inhibitors (selegiline and rasagiline), or anticholinergics (trihexyphenidyl and procyclidine), or fixed

combination with carbidopa and entacapone, a catechol-O-methyltransferase inhibitor.[4] These adjunct drugs prevent rapid metabolism of levodopa into dopamine, which has a short plasma half-life of 1.5 hours, thereby improving the bioavailability of levodopa and reducing peripheral side effects associated with levodopa treatment such as nausea and vomiting. The most common early side effects associated with levodopa include nausea, somnolence, dizziness, and headache. Long-term administration may lead to confusion, hallucinations, delusions, agitation, psychosis, and orthostatic hypotension, particularly in older patients.[4,8]

Another class of dopaminergic drugs used to treat motor symptoms includes dopamine receptor agonists, which are thought to activate post-synaptic dopamine receptors and are considered second-line treatment due to varied effectiveness. In Canada, commonly prescribed dopamine receptor agonists include non-ergoline dopamine receptor agonists such as ropinirole, pramipexole, and rotigotine as well as ergoline dopamine receptor agonists such as bromocriptine, either as monotherapy or in combinational therapy with levodopa.[4,8] According to the Canadian Guidelines on Parkinson's Disease, dopamine receptor agonists are commonly used in early PD but restricted in patients older than 70.[7] Varying degrees of adverse events (AEs) associated with the dopaminergic system are reported, which occur at a greater rate and severity than with levodopa treatment and may include somnolence, pathological gambling, neuroleptic malignant syndrome, hypotension, and nausea/vomiting.[4,8] Patients on ergoline dopamine agonists require monitoring due to the risk of pleuropulmonary and cardiac valve fibrosis.[7]

Despite the efficacy of levodopa in most PD patients, 20% to 75% of PD patients develop motor complications after three to five years of treatment; these complications may remain for up to 50% of the waking day.[4] The controlled-release formulation of levodopa/carbidopa is often offered in more severe cases to manage motor fluctuations and "wearing off" episodes; however, this treatment is limited by potential erratic absorption and delayed response.[4,8] Other types of drugs can be administered as an adjunct to levodopa in an attempt to reduce "off" time.[7] Monoamine oxidase type B inhibitors, such as rasagiline and selegiline, prevent the metabolism of dopamine in the brain.[7] Catechol-O-methyltransferase inhibitors, such as entacapone, increase bioavailability of levodopa in the periphery.[7] Anticholinergics, such as trihexyphenidyl and benztropine, are mostly used in patients with tremor; lack of effectiveness and neuropsychiatric side effects limit their use in older patients.[7]

A more invasive option for patients with inadequate management of motor complications by optimized standard therapies is continuous enteral infusion of levodopa/carbidopa in a gel formulation (marketed as DUODOPA in Canada). The levodopa/carbidopa intestinal gel ensures a stable and continuous plasma concentration of levodopa thereby reducing severe and debilitating motor fluctuations. However, side effects associated with the invasive percutaneous route of administration, device-related complications, and usage of health care resources limit its use among advanced PD patients.[4,8] Finally, deep brain stimulation is an invasive stereotactic brain surgery that has few but potentially serious risks and is generally not performed in older patients or those with neuropsychiatric features.[4] Therefore, the optimization of oral anti-PD medications remains the most common treatment option, particularly among advanced PD patients, with a constant challenge to ensure adequate plasma dopamine level and management of symptoms during the unpredictable "off" or drug "wearing off" episodes.

Drug

Apomorphine hydrochloride, a synthetic derivative of morphine without any of the narcotic and opiate effects of the parent compound, is marketed in Canada as Movapo. It is formulated in 2 mL ampoules or 3 mL pre-filled disposable multi-dose pens with a concentration of 10 mg/mL. Apomorphine should be administered as subcutaneous injection in the upper arms, thighs, or abdomen and given as an adjunct to oral anti-PD medications. Treatment with apomorphine is recommended with a starting dose of 2 mg up to a maximum of 6 mg based on effectiveness and tolerance, with the titration being done ideally by a health care professional, after which patients or their caregivers may administer the prescribed dose as instructed to treat recurring "off" episodes. Dose titration should be done under close medical supervision, and blood pressure should be monitored in both sitting and standing positions every 20 minutes post-dose up to 60 minutes (unless no significant hypotension ensues). During dose titration, a 0.2 mL (2 mg) increment to the next higher dose or 0.1 mL (1 mg) reduction to the next lower dose may be given at least two hours after the previous dose, at the next observed "off" event, depending on tolerability and effectiveness. The maintenance dose during outpatient use should be 0.1 mL (1 mg) lower than the highest tolerated test dose.[9] The Health Canada–approved indication for apomorphine is to treat acute, intermittent hypomobility "off" episodes ("end-of-dose wearing off" and unpredictable "on/off") in patients with advanced PD.

Apomorphine is found to be a highly potent non-ergoline D_1 D_2 dopamine agonist and relatively non-selective at D_1, D_2, D_3, D_4, and D_5 receptors due to its chemical structure resembling dopamine. The mechanism of action of apomorphine is unknown, but it is thought to stimulate post-synaptic D_2 type receptors in the caudate nucleus and putamen.[4,9,10] Table 2 provides details about the mechanism of action, indication, route and dose of administration, and side effects of apomorphine and other non-ergoline dopamine agonists.

Table 2: Key Characteristics of Apomorphine, Rotigotine, Ropinirole, and Pramipexole

	Apomorphine	Rotigotine	Ropinirole	Pramipexole
Mechanism of Action	Non-ergoline dopamine agonist believed to stimulate D_2 receptors of the caudate-putamen	Non-ergoline dopamine agonist believed to increase the activities of the D_3, D_2, and D_1 receptors of the caudate-putamen	Non-ergoline dopamine agonist believed to stimulate D_2 receptors of the caudate-putamen	Non-ergoline dopamine agonist believe to stimulate D_2 receptors of the caudate-putamen
Indication[a]	The acute, intermittent treatment of hypomobility "off" episodes ("end-of-dose wearing off" and unpredictable "on/off") in patients with advanced PD	The treatment of signs and symptoms of idiopathic PD; can be used both as early therapy without concomitant levodopa and as an adjunct to levodopa	The treatment of signs and symptoms of idiopathic PD; can be used both as early therapy without concomitant levodopa and as an adjunct to levodopa	The treatment of signs and symptoms of idiopathic PD; can be used both as early therapy without concomitant levodopa and as an adjunct to levodopa
Route of Administration	Subcutaneous	Transdermal	Oral	Oral
Recommended Dose	The drug is administered intermittently as needed.	Early-stage PD: A single daily dose should be initiated at 2 mg/24h and then	The recommended starting dosage is 0.25 mg three times daily. Based on individual patient response, dosage should then be	Dosages should be increased gradually from a starting dose of 0.375 mg/day given in three divided doses and

	Apomorphine	Rotigotine	Ropinirole	Pramipexole
	The initial recommended dose is 2 mg with titration of up to a maximum individual dose of 6 mg. The recommended maximum daily dose is 20 mg.	increased in weekly increments of 2 mg/24 h to an effective dose up to a maximal dose of 8 mg/24 h. Advanced-stage PD: A single daily dose should be initiated at 4 mg/24 h and then increased in weekly increments of 2 mg/24 h to an effective dose up to a maximal dose of 16 mg/24 h.	titrated by weekly increments of 0.25 mg per dose. After week 4, daily dosage may be increased by 0.5 mg to 1.0 mg per dose on a weekly basis until an optimal therapeutic response is established. The recommended maximum dose is 18 mg/day in patients receiving regular dialysis. Patients with severe renal impairment (creatinine clearance less than 30 mL/min without regular dialysis) have not been studied, and administration of ropinirole to such patients is not recommended.	should not be increased more frequently than every 5 to 7 days. The maximal recommended dose is 4.5 mg per day. In patients with a creatinine clearance between 30 mL/min and 50 mL/min, the initial daily dose should be administered in two divided doses, starting at 0.125 mg twice a day (0.25 mg daily). A maximum daily dose of 2.25 mg should not be exceeded. In patients with a creatinine clearance between 15 mL/min and 30 mL/min, the daily dose should be administered in a single dose, starting at 0.125 mg daily. A maximum daily dose of 1.5 mg should not be exceeded.
Serious Side Effects / Safety Issues	Warning/precautions: sudden onset of sleep	Warning/precautions: sudden onset of sleep	Warning/precautions: sudden onset of sleep	Warning/precautions: sudden onset of sleep and somnolence

PD = Parkinson's disease.

[a] Health Canada indication.

Source: Movapo (apomorphine),[9] Neupro (rotigotine),[11] Requip (ropinirole),[12] and Mirapex (pramipexole)[13] product monographs.

Objectives and Methods

Objectives

To perform a systematic review of the beneficial and harmful effects of apomorphine hydrochloride injection (Movapo) for the acute, intermittent treatment of hypomobility "off" episodes ("end-of-dose wearing off" and unpredictable "on/off" episodes) in patients with advanced PD.

Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Phase III studies were selected for inclusion based on the selection criteria presented in Table 3.

Table 3: Inclusion Criteria for the Systematic Review

Patient Population	Adult (>18 years) patients with advanced PD[a] Subgroups: • Baseline severity of PD (based on UPDRS score, "off" states, H&Y scale for staging the severity of Parkinson's disease, etc.) • Baseline oral medications for PD • Type of "off" episodes (e.g., "wearing off," "morning off," or "unpredictable off" episodes)
Intervention	Apomorphine as per Health Canada–approved product monograph,[b] added to background oral medications for PD used as monotherapy or combination therapy[c] • Starting dose: 0.2 mL (2 mg), SC injection • 0.1 mL (1 mg) increments every few days during the titration if needed • Titrated up to a maximum dose of 0.6 mL (6 mg) • Retreatment should not be started within 2 hours after last dose, if needed
Comparators	Placebo added to oral medications for PD used as monotherapy or combination therapy,[c] such as: • Levodopa (levodopa/carbidopa or levodopa/benserazide, with or without COMT inhibitors) • Dopamine agonists • MAO-B inhibitors • Amantadine
Outcomes	**Key efficacy outcomes:** • Mobility (or hypomobility) by validated measure (e.g., UPDRS motor score, Dyskinesia Rating Scale, hand-tapping test scores, step-seconds test scores, etc.)[d] • Duration of "off" episodes (duration of each "off" episode, sum of time "off" episodes per day, etc.)[d] • HRQoL[d] • Symptom reduction (e.g., tremor, bradykinesia, rigidity, and postural instability)[d,e] **Other outcomes** • Time to response (interval between injection and declared recovery) • Frequency of "off" events (number of "off" events) • Proportion of injections declared to have aborted the "off" event (one proportion calculated for each patient) • Proportion of inability of self-injection • Proportion of non-response of injections • Use of health care services (hospitalization, physician office visits, etc.)

	Harms outcomes: AEs, SAEs, WDAEs, mortality, and notable harms/harms of special interest (dyskinesia, injection site reaction, postural hypotension, impulsive/asocial behaviour, etc.)
Study Design	Published and unpublished phase III RCTs

AE = adverse event; COMT = catechol-O-methyl transferase; H&Y = Hoehn and Yahr; HRQoL = health-related quality of life; MAO-B = monoamine oxidase type B; PD = Parkinson's disease; RCT = randomized controlled trial; SAE = serious adverse event; SC = subcutaneous; UPDRS = Unified Parkinson's Disease Rating Scale; WDAE = withdrawal due to adverse event.

[a] Apomorphine hydrochloride injection (MOVAPO) indicated for the acute, intermittent treatment of hypomobility "off" episodes ("end-of-dose wearing off" and unpredictable "on/off" episodes) in patients with advanced Parkinson's disease.[9] It is the only treatment that specifically targets predictable and unpredictable "off" episodes and is thus used as adjuvant therapy to existing advanced Parkinson's disease treatment.[14]

[b] The recommended starting dose of MOVAPO is 0.2 mL (2 mg). Titrate on the basis of effectiveness and tolerance, up to a maximum recommended dose of 0.6 mL (6 mg). In controlled trials, doses greater than 0.6 mL (6 mg) did not lead to an increased effect and, therefore, individual doses above 0.6 mL (6 mg) are not recommended. Retreatment and treatment discontinuation: If a single dose of MOVAPO is ineffective for a particular "off" period, a second dose should not be given for that "off" episode. The efficacy and safety of administrating a second dose for a single "off" episode has not been studied systematically. Do not administer a repeat dose of MOVAPO sooner than 2 hours after the last dose. If the patient tolerates the 0.2 mL (2 mg) dose, and responds adequately, the starting dose should be 0.2 mL (2 mg), used on an as-needed basis to treat recurring "off" episodes. If needed, the dose can be increased in 0.1 mL (1 mg) increments every few days on an outpatient basis.

[c] Oral medications for PD in Canada: Levodopa including levodopa/carbidopa — immediate release, levodopa/benserazide — immediate release; dopamine agonists including pramipexole, ropinirole, and bromocriptine; MAO-B inhibitors including rasagiline and selegiline); COMT inhibitors including tolcapone and entacapone.[7] Standard therapies available in Canada may include drug and non-drug.[7]

[d] Identified as an important outcome in the patient input submission to CADTH Common Drug Review.

[e] Cardinal features of PD (symptoms) are tremor, bradykinesia, rigidity, and postural instability.

The literature search was performed by an information specialist using a peer-reviewed search strategy. Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates via Ovid, Embase (1974–) via Ovid, and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Movapo (apomorphine) and Parkinson's disease.

Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and controlled clinical trials. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on August 2, 2017. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee on December 13, 2017. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters* checklist (https://www.cadth.ca/grey-matters): Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Drug and Device Regulatory Approvals, Advisories and Warnings, Drug Class Reviews, Databases (Free), Internet Search, and Open Access Journals. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

CADTH

Two CADTH Common Drug Review (CDR) clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 4; the excluded studies (with reasons) are presented in Appendix 3.

Service Line: CADTH Common Drug Review
Version: Final
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Results

Findings From the Literature

A total of 256 studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 4 and described in Section 3.2. A list of excluded studies is presented in Appendix 3.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

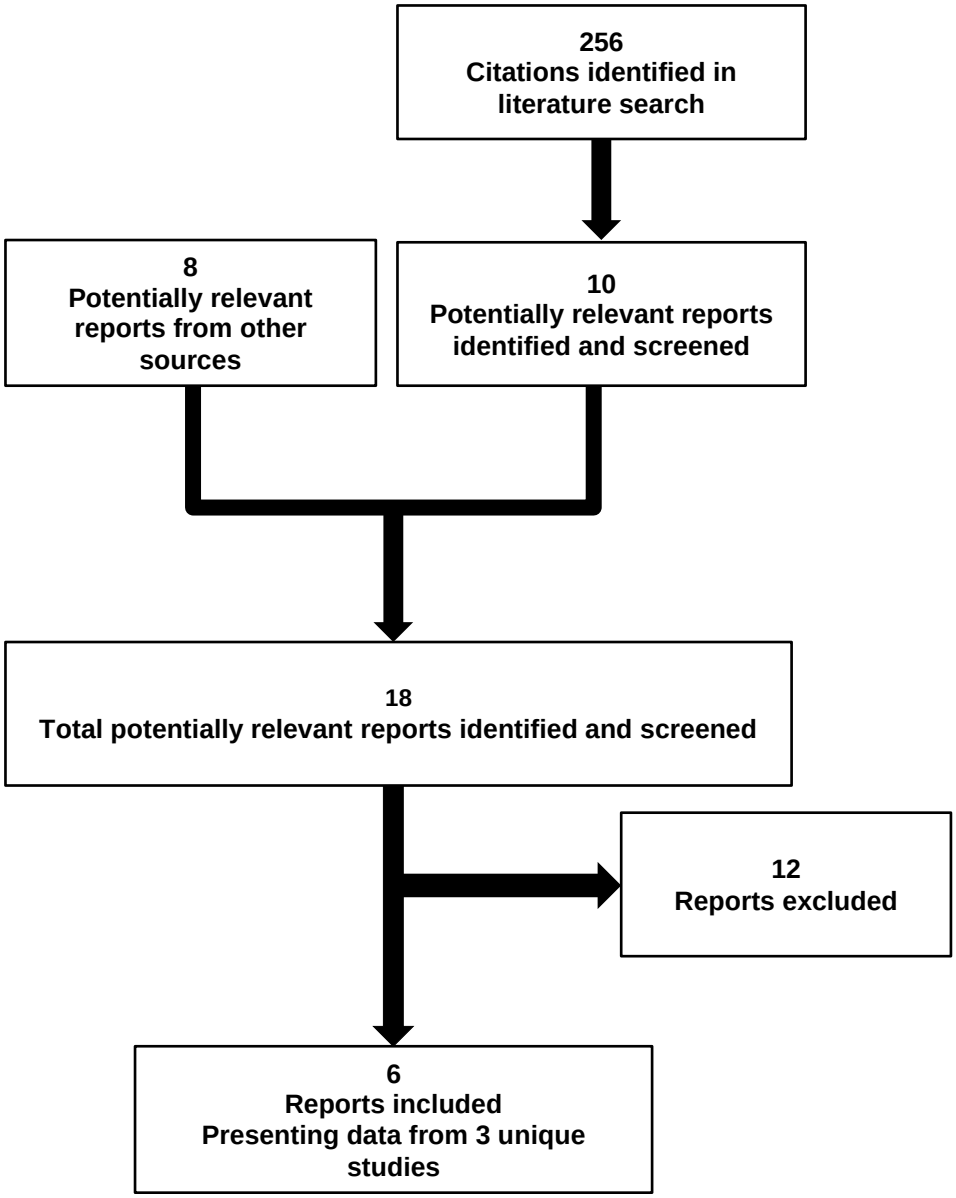


Table 4: Details of Included Studies

		Study 202	Study 301	Study 302
Designs and Populations	**Study Design**	DB RCT (phase II)	DB (crossover) RCT (phase III)	DB RCT (phase III)
	Locations	3 centres in the US	2 centres in the UK	26 centres in the US
	Randomized (N)	29	17	62
	Inclusion Criteria	- Age 30 to 80 years - Patients with advanced idiopathic PD - Experienced at least one “off” episode and averaging at least 2 hours daily “off” state (either “on/off” or “wearing off” patterns) despite optimal treatment with at least two drugs (typically carbidopa/levodopa with a direct dopamine agonist) for at least 30 days. - Classified as stage 2 to 4 of the H&Y scale for staging the severity of PD	- Adult (≥ 18 years) patients with idiopathic PD - Classified as stage 2 to 4 of the H&Y scale for staging the severity of PD - Patients must have been on an optimally maximized oral anti-PD medication including levodopa/decarboxylase inhibitors for at least 30 days before randomization - Patients must have been receiving APO SCI for rescue therapy for “off” events for a duration of at least three months - Patients must have been injecting at least 2 bolus doses of ≤ 10 mg of APO per day for the week prior to the study	- Adult (≥ 18 years) patients with idiopathic PD - Classified as stage 2 to 4 of the H&Y scale for staging the severity of PD - Patients must have been on an optimally maximized oral anti-PD medication - Patients must have been receiving APO SCI for rescue therapy for “off” events for a duration of at least three months - Patients must have been injecting at least 2 doses of APO per day for the week prior to the study - Patients participating in study APO 401[15]
	Exclusion Criteria	- Patients who had received APO previously - Patients with psychoses or dementia existing concurrently or in a medical history - Patients with unstable and clinically significant disease, e.g. orthostatic hypotension - Patients undergoing treatment with neuroleptic drugs or over-the-counter antihistaminic preparations	- Patients under medical therapy for clinically significant psychoses or dementia - Patients with unstable and clinically significant disease - Patients whose APO regimen is by continuous infusion or by administration methods other than intermittent SCI	- Patients under medical therapy for clinically significant psychoses or dementia - Patients with unstable and clinically significant disease - Patients treated with APO by administration methods other than intermittent SCI
Drugs	**Intervention**	APO SCI Initial dose: 0.2 mL (2 mg) to 1 mL (10mg) Up to 5 times SCI /day Maximum daily dose: 50 mg	APO SCI The injected dose was set equal to that typically used by the patient before study entry.	APO SCI There were two intervention arms: APO at the typically effective dose; APO at the typically effective dose + 0.2 mL (2.0 mg). The maximum allowed dose was 1.0 mL (10.0 mg) for a single injection or 50 mg as a daily dose.

		Study 202	Study 301	Study 302
	Comparator(s)	Placebo	Placebo	Placebo Note: There were two comparator arms: placebo; placebo + 0.2 mL.
DURATION	**Phase**			
	Run-in	None	None	None
	Double-blind	4 weeks	2 days	1 day
	Follow-up	None	None	None
	Open-label	None	None	None
OUTCOMES	**Primary End Point**	UPDRS-III score 15 minutes to 20 minutes after dosing or "on-state" occurred (on day 2 , in-patient phase)	UPDRS-III score 20 minutes post-dose	UPDRS-III score 20 minutes post-dose
	Other End Points	*Secondary outcomes:* In-patient phase - Hand-tapping test - Webster step-seconds test - Dyskinesia Rating Scale Outpatient phase - Interval (minutes) between injection and declared recovery - Proportion of injections declared to have aborted the "off" event (one proportion calculated for each patient) - Sum of hours "off" per day AEs - Complete physical exam including weight, 12-lead ECG, and clinical laboratory evaluations - Vital signs (pulse, respiration, blood pressure, and temperature while resting) - Any AE	*Secondary outcomes*: - Change in UPDRS-III score at 10 minutes and 60 minutes, AUC for UPDRS-III scores at 10, 20, and 60 minutes - Dyskinesia Rating Scale scores at 10, 20, and 60 minutes - Patient-declared time to "off" state relief AEs - Any AE - Physical exam - Vital signs	*Secondary outcomes:* - Change in UPDRS-III score at 10 minutes and 90 minutes - Per cent change in UPDRS motor scores at 10, 20, and 90 minutes - UPDRS-III AUC at 10, 20, and 90 minutes - Time to patient-declared onset of relief (maximum observation time = 40 minutes) - Change in Webster step-seconds test score from pre-dose to 2.5, 5, 7.5, 10, 15, 20, 40, and 90 minutes after dosing - Change in dyskinesia assessment from pre-dose to 10, 20, and 90 minutes after dosing AEs - Any AE - Physical exam - Vital signs - Orthostatic hypotension
NOTES	**Publications**	Dewey, Jr. et al. (2001)[16]	None	Pfeiffer et al. (2007)[17]

AE = adverse event; APO = apomorphine; AUC = area under the curve; CSR = Clinical Study Report; DB = double blind; ECG = electrocardiogram; H&Y = Hoehn and Yahr; RCT = randomized controlled trial; PD = Parkinson's disease; SCI = subcutaneous injections; UPDRS-III = Unified Parkinson's Disease Rating Scale, Part III.

Source: Study 202 CSR,[1] Study 301 CSR,[2] Study 302 CSR.[3]

Included Studies

Description of Studies

One phase II and two phase III randomized controlled trials were included in the CDR systematic review, all of which were placebo-controlled and considered pivotal by Health Canada (Table 4).

All three trials included in this report, APO 202, APO 301, and APO 302, were prospective, double-blind, randomized, placebo-controlled, multi-centre studies. APO 202 and APO 302 had a parallel-group design and APO 301 had a crossover design. APO 301 was conducted in the UK; the other two trials were done in the US. APO 301 and APO 302 were phase III trials, whereas APO 202 was a phase II trial. APO 202 was designed to assess the therapeutic response to subcutaneous apomorphine in both in-patient and outpatient settings among apomorphine-naive patients. APO 301 and APO 302 trials aimed to measure the continued efficacy in patients who were on apomorphine treatment for at least three months. All three trials were conducted in advanced PD patients, defined as stage 2 to 4 in the Hoehn and Yahr (H&Y) scale.

APO 202 (N = 29, randomization ratio 2:1 for apomorphine and placebo) had two phases: an in-patient dose-titration phase followed by a one-month outpatient treatment phase. Dosage to reverse “off” states induced by withholding normal anti-PD medications was determined in the in-patient phase, and apomorphine was used to treat spontaneous “off” episodes as needed in the outpatient phase. During the first in-patient visits, an unblinded dopaminergic challenge test to determine dopamine responsiveness was performed, followed by a second visit where upwardly titrated doses (2 mg to 10 mg) of apomorphine were given until a therapeutically equivalent response (TED, defined as ≥ 90% of the response elicited by levodopa treatment) was reached. The TED was then continued for a month in an outpatient setting to reverse “off” episodes as needed.

APO 301 (N = 17) consisted of two crossover visits where patients were randomized to receive either a typically effective dose of apomorphine or placebo on separate days in response to spontaneous “off” episodes occurring at least one hour after administration of typical morning dose of oral anti-PD medications. APO 302 (N = 62, randomization ratio 2:2:1:1) was part of a larger open-label safety trial, APO 401, where four groups of patients were treated on a single day after the onset of spontaneous “off” episodes with apomorphine or placebo at the patient’s typically effective dose or their typically effective dose plus 2 mg. The typically effective dose in both trials was determined from more than three months of apomorphine treatment before the start of the study.

Patients in all three trials were on optimal anti-PD medications including levodopa and were asked to take trimethobenzamide as an antiemetic to minimize nausea. The follow-up duration for the APO 202 treatment phase was four weeks, whereas in APO 301 and 302, treatment phases lasted for two and one visits, respectively. The study designs of these studies are illustrated in Figure 2, Figure 3 and Figure 4 (Appendix 4).

Populations

Inclusion and Exclusion Criteria

Please refer to Table 4 for a detailed list of inclusion and exclusion criteria in the included trials.

Across all three trials, patients with advanced idiopathic PD, classified as stages 2 to 4 in the H&Y scale, who were on an optimally maximized oral therapy regimen (levodopa/carbidopa in addition to at least one or dopamine agonist) were included. Patients in the APO 202 trial were apomorphine naive and experienced daily episodes of refractory motor fluctuations (at least one daily "off" episode and at least two hours of daily "off" time). The APO 301 and 302 trials, on the other hand, included patients who were on subcutaneous apomorphine treatment for at least three months in response to "off" episodes before study enrolment, with an average of at least two bolus doses of ≤ 10 mg of apomorphine per day for the week prior to study initiation.

Patients were excluded from all three trials if they had any of the following: history of drug or alcohol dependency; unstable and clinically significant diseases including psychoses and dementia; cardiovascular (including orthostatic hypotension), hematologic, hepatic, renal, metabolic, respiratory, gastrointestinal or endocrine systems or neoplasms; and allergy to morphine or its derivatives. APO 202 also excluded patients on apomorphine, neuroleptic drugs, or methyldopa, and those treated with stereotactic surgery. Patients in the APO 301 and APO 302 trials were excluded if they took apomorphine by any method other than intermittent subcutaneous injection. Patients in the APO 202 trial were also excluded from participating if they did not have a significant improvement (≥ 30%) in the Unified Parkinson's Disease Rating Scale, Part III (UPDRS-III), motor score following administration of oral levodopa during the dopaminergic challenge test.

Baseline Characteristics

A summary of the demographic and baseline characteristics in the trials is given in Table 5. Overall, patient characteristics were similar between treatment groups within each study except for the percentage of males and females in APO 202 and APO 301 and age at onset of PD in APO 202. The participants had a mean age of greater than 60 years (range, 61 to 66 years), were predominantly male (range, 60% to 89%), Caucasian (range, 93% to 100%), non-smoking (range, 50% to 78%), and non-alcohol-using (range, 50% to 100%). Patients had a mean duration of PD of 9 to 16 years at baseline with an age of onset of around 50 years. Participants in the APO 202 trial spent a daily average of close to six hours in the "off" state. Although the groups within the trials were similar with regard to mean baseline UPDRS-III score, the score varied among participants across the trials. In APO 202 and APO 301, baseline UPDRS-III assessments were done in the pre-dose "off" state, whereas in APO 302 assessment was done during the "on" state, hence the noticeably lower values in these patients. Mean effective apomorphine dose was reported only in the APO 302 trial and ranged from about 3 mg to 4 mg between the groups, and participants were exposed to apomorphine for an average of around 430 days prior to study initiation. Daily levodopa dose at baseline was reported only in the APO 202 trial and was similar between the groups, ranging from 776 mg in the apomorphine treatment group to 819 mg in the placebo group.

Table 5: Demographic and Baseline Characteristics (ITT)

Baseline Characteristics	Study APO 202		Study APO 301		Study APO 302	
	APO (N = 20)	PLB (N = 9)	APO/PLB (N = 8)	PLB/APO (N = 9)	Pooled APO (N = 35)	Pooled PLB (N = 27)
Age (years), mean (SE)	66.1 (2.0)	61.6 (3.7)	61.38 (2.7)	62.0 (2.1)	64.8 (1.5)	66.5 (1.9)
Sex, n (%)						
Male	12 (60.0)	8 (88.9)	6 (75.0)	6 (66.7)	25 (71.4)	20 (74.1)
Female	8 (40.0)	1 (11.1)	2 (25.0)	3 (33.3)	10 (28.6)	7 (25.9)
Race, n (%)						
Caucasian	19 (95.0)	8 (88.9)	8 (100)	9 (100)	35 (100)	25 (92.6)
Other	1 (5.0)	1 (11.1)	0	0	0	2 (7.4)
PD duration (years), mean (SE)	9.2 (1.1)	12.3 (2.1)	14.0 (1.2)	13.4 (2.1)	13[a]	16[a]
Age at onset of PD (years), mean (SE)	57 (3)	49 (4)	NR	NR	51.1 (1.4)	50.4 (2.6)
Tobacco use, n (%)						
None or rare	12 (60.0)	7 (77.8)	4 (50.0)	5 (55.6)	21 (60.0)	15 (55.6)
Former user	7 (35.0)	2 (22.2)	3 (37.5)	2 (22.2)	12 (34.3) (> 1 yr)	11 (40.7)
Current user	1 (5.0)	0 (0.0)	1 (12.5)	2 (22.2)	2 (5. 7)	1 (3. 7)
Alcohol use, n (%)						
None or rare	19 (95.0)	9 (100.0)	4 (50.0)	4 (44.4)	28 (80.0)	17 (63.0)
Moderate use	1 (5.0)	0 (0.0)	4 (50.0)	5 (55.6)	7 (20.0)	10 (37.0)
Time in "off" state (hours/day), mean (SE)	5.8 (0.5)	5.8 (0.8)	NR	NR	NR	NR
Daily levodopa dose in mg/d IR equivalents, mean (SE)	776 (98)	819 (146)	NA	NA	NA	NA
Days on APO, mean (SE)	NA	NA	NR	NR	426 (32)	444 (32)
Typically effective APO dose in mg, mean (SE)	NA	NA	NR	NR	4.2 (0.3)	3.3 (0.3)
UPDRS-III score, mean (SE)						
Pre-dose "off" state	39.7 (2.0)	36.3 (2.3)	41.3 (2.5)	40.1(2.2)	NR	NR
Baseline "on" state	NR	NR	NR	NR	25.6 (2.0)	19.4 (2.4)

APO = apomorphine; CSR = Clinical Study Report; IR = immediate release; ITT = intention-to-treat; NA = not applicable; NR = not reported; PD = Parkinson's disease; PLB = placebo; SE = standard error; UPDRS = Unified Parkinson's Disease Rating Scale.

Note: Pooled APO includes patients who received APO in their typically effective dose or typically effective dose + 0.2 mL; pooled PLB includes patients who received PLB volume-matched to APO or PLB + 0.2 mL.

[a] Not reported in the CSR; calculated by CADTH by subtracting mean age from mean age at onset of PD.

Source: APO 202,[16] Study 202 CSR,[1] Study 301 CSR,[2] APO 302,[17] Study 302 CSR.[3]

Interventions

In the APO 202 trial, an in-patient phase was conducted consisting of two visits. The first visit was to determine the dopaminergic response of patients; those with a UPDRS-III motor score difference of more than 30% between the pre-dose "off" state and post-dose "on" state were considered dopamine responsive and were allowed to continue in the study. On the second visit, dose titration was done to find the optimal apomorphine dose required to reverse "off" episodes. During the in-patient visits, patients had to withhold their regular overnight or morning doses of levodopa and dopamine agonists to precipitate "off" episodes, after which optimal doses of levodopa (immediate-release levodopa) or apomorphine were administered. Dose titration was performed by escalating doses of subcutaneous apomorphine or pH and volume-matched placebo from 2 mg to 10 mg with 2 mg increments in response to separate "off" episodes spaced by at least two hours. Dose escalation was stopped at 10 mg or upon demonstration of therapeutically equivalent response, defined as a change in the UPDRS score that was at least 90% of that elicited by oral levodopa. The TED (mean, 5.4 mg/dose) of apomorphine or equivalent placebo was continued during the outpatient phase for four weeks in parallel groups to reverse spontaneous "off" episodes as needed, and patients self-administered the injections. One dose adjustment was allowed after two weeks of outpatient use if needed, but no crossover of treatment was permitted. A maximum of five doses per day was allowed during the outpatient phase, which equated to a daily maximum of 50 mg of apomorphine (mean, 5.8 mg/dose) or equivalent placebo.

In the APO 301 and APO 302 trials, patients continued to receive doses that had been typically used for at least three months before study entry. In APO 301, patients were randomized to administer either subcutaneous apomorphine (mean, 3.9 mg/dose; range, 2 mg to 10 mg) or pH-matched and volume-matched placebo in a crossover fashion on two alternate visits in response to the first documented "off" episode (defined as significant immobility or UPDRS-III motor score ≥ 32) at least one hour after their usual morning dose of anti-PD medications. The APO 302 trial had a similar dosing regimen (range, 1.5 mg/dose to 10 mg/dose) but in parallel groups with a maximum of 10 mg per dose and a maximum of 50 mg per day. In contrast to APO 301, the dosing in APO 302 was administered on a single day in the following four groups of patients randomized in a 2:2:1:1 ratio:

- apomorphine at the patient's typically effective dose (apomorphine: mean dose, 4.6 mg; range, 2 mg to 10 mg)
- apomorphine at the patient's typically effective dose plus 2 mg (apomorphine + 2: mean dose, 5.8 mg; range, 3.5 mg to 10 mg)
- volume-matched placebo equal to the patient's typically effective dose
- volume-matched placebo equal to the patient's typically effective dose plus 2 mg (placebo + 2).

Patients in all studies were on a stable (defined as taken for ≥ 30 days) and optimized anti-PD medication regimen that included levodopa,[1] levodopa/decarboxylase inhibitors,[2] levodopa/carbidopa inhibitors,[3] and at least one other drug (oral dopamine agonist, e.g., anticholinergics, catechol-O-methyltransferase inhibitors) except methyldopa. All patients were instructed to take oral trimethobenzamide 250 mg three times daily to minimize nausea

at least three days before apomorphine treatment initiation and throughout the study, with the option of starting, continuing, or adjusting trimethobenzamide dosing. Other notable concomitant non-anti-PD medications included antidepressants, antipsychotic drugs, contraception, and any permissible medications to maintain patients' comfort and well-being.

Outcomes

Efficacy

The primary efficacy outcome across all three trials was the UPDRS-III motor score measured at pre-dose "off" state and at different time points during post-dose "on" state. The change in UPDRS-III motor score from pre-dose to 15 to 20 minutes post-dose during the in-patient phase of APO 202 and to 20 minutes post-dose in APO 301 and APO 302 was the primary efficacy outcome. The UPDRS is a widely used tool to measure disease severity and treatment efficacy in PD patients and consists of four parts. The motor examination comprises 14 items designed to assess speech, tremors, rigidity, and repeated movements (e.g., rapidly alternating movements of the hands), as well as gait, postural stability, and other kinetic parameters. Each item is rated on a 0 to 4 scale, with total score ranging from 0 (no disability) to 56 (highest disability). The UPDRS motor examination has been shown to have acceptable validity and reliability, and a minimal clinically important difference (MCID) of −5 points to −6.5 points has been reported in advanced PD patients.[18-26]

The secondary efficacy outcomes varied by trial and involved combinations of the following: an assessment of the UPDRS-III motor score at various time points, hand-tapping test (HTT) score (the number of taps alternating between two counters done with one hand within 60 seconds), Webster step-seconds test (WSST) score (the number of steps taken with the right foot multiplied by the time to complete a 15-foot round-trip walk, starting from and ending in a sitting position), Dyskinesia Rating Scale (DRS) score (types and severity of dyskinesia on a scale of 0 to 4 when asked to walk, drink from a cup, and put on a coat and button it), and patient diaries to record information about "on" and "off" episodes (frequency, duration, time to onset, number of injections, and recovery from perceived "off" episodes).[1-3] Other than the UPDRS, there was no evidence demonstrating the validity and reliability of the other measures in PD patients except for the DRS. In addition, an MCID was not found for these outcomes apart from diary-recorded "off" time, which ranged from 1.0 to 1.8 hours.

In the APO 202 trial, the following secondary end points were assessed during the in-patient phase in the following order: HTT score, WSST score, and DRS score. During the outpatient phase, diaries maintained by patients or caregivers were used to calculate the following end points: interval between injection and point of self-declared recovery by the patients, per cent of injections where "off" state was successfully aborted, daily hours spent in "off" and "on" states, awake time, time on with dyskinesias, time of meals, and oral medication ingestion.

In APO 301 and APO 302, the time-course of apomorphine dosing was performed by measuring UPDRS-III motor score at three time points (10, 20, and 60 or 90 minutes post-dose). Dyskinesia was assessed at the same time points as UPDRS-III motor score using DRS in both trials. Time of onset was recorded by patients' self-report or modified WSST (stopped at 60 seconds) at one and seven time points (2.5, 5, 7.5, 10, 15, 20, and 40 minutes post-dose) in APO 301 and APO 302, respectively.

Harms

In all trials, routine physical examinations, vital signs (pulse, respiration, blood pressure, and temperature), clinical laboratory tests (hematology, serum chemistry, urinalysis), and electrocardiograms (12 leads) were performed at study enrolment, following treatment evaluation during follow-up visits or at study exit. Orthostatic monitoring was conducted in APO 302 only, and the incidence of orthostatic hypotension was recorded in case of a drop of ≥ 20 mm Hg in systolic blood pressure (SBP) or ≥ 10 mm Hg in diastolic blood pressure (DBP) (criterion 1), or a drop of ≥ 30 mm Hg in SBP or ≥ 20 mm Hg in DBP (criterion 2) from a sitting to a standing position.[3] Any AEs were documented using open-ended questions following each dosing and study visit. An AE was defined as any unfavourable and unintended medical occurrence in a patient following the administration of a pharmaceutical product, which did not necessarily have a causal relationship with the treatment. A serious adverse event (SAE) was defined as any untoward medical signs and symptoms that resulted in death, in-patient hospitalization or prolongation of existing hospitalization, or persistent or significant disability/incapacity, was life threatening, or was an otherwise significant event. The onset, duration, and severity of all AEs were recorded and were further categorized based on relatedness to study drug.

Statistical Analysis

In the APO 202 trial, changes in UPDRS-III motor score and HTT score from pre-dose to post-dose were analyzed using analysis of covariance (ANCOVA) with the “off”-state score as a covariate and treatment group as a factor. All other secondary in-patient efficacy outcomes and all outpatient outcomes were tested using non-parametric tests. Changes in WSST and DRS scores were analyzed by the Wilcoxon rank sum test. For three outcomes (UPDRS-III motor score, HTT, WSST), response ratio (per cent change in score after apomorphine injection divided by per cent change in score after dopaminergic challenge) was calculated and analyzed using analysis of variance (ANOVA) with treatment group as a factor or Wilcoxon rank sum test if normality assumptions were not met. In addition, per cent change was calculated for each score (100 × [“on” score − “off” score] / “off” score), which was then analyzed using ANCOVA with treatment as a factor and the “off”-state score as a covariate. All end points analyzed for the in-patient phase were done in the safety/ITT (intention-to-treat) population, whereas end points for the outpatient phase were analyzed in the secondary efficacy population (defined as those who continued into the outpatient phase of study). No adjustment or imputation for missing observations was done for patients who failed to progress into the outpatient phase. No interim analyses were planned or performed.

In the APO 301 trial, the primary and secondary end points involving changes in UPDRS motor score from pre-dose to 10, 20, and 60 minutes post-dose were analyzed using a repeated-measures ANCOVA model with the terms sequence (order in which apomorphine or placebo was given), subject within sequence, pre-dose score, treatment, and period (time after dose). Since the study was crossover in design, the sequence effect was tested using the subject within sequence mean square as the error term. Further testing was done for period effect and treatment-period interaction, and in the case of a significant treatment-period interaction, data from day 1 only were analyzed as a parallel study design. The time to self-reported significant symptom relief following injection was analyzed using the Wilcoxon signed rank test, and a value of 60 minutes was imputed for those without any relief within the observation period. An additional analysis using repeated-measures ANOVA with the terms sequence, subject within sequence, treatment, and period was done to compare the time to response between the two treatment groups, excluding patients who did not report an onset of symptom relief. Change in dyskinesia severity was analyzed using the Wilcoxon signed rank test.

Data in the APO 302 trial was tested for normality using the Shapiro–Wilk test and Kolmogorov–Smirnov test, and non-parametric analyses were conducted if the normality assumptions were not met or as confirmatory analyses even if data were normally distributed. The primary end point as well as other end points involving the UPDRS-III measurement at different time points were analyzed using an ANCOVA model with the term treatment and pre-dose motor score as covariates. All four treatment groups (apomorphine, apomorphine + 2, placebo, placebo + 2) were included in the model. The primary contrast was done between pooled apomorphine group and pooled placebo group, which was further confirmed using the covariance-adjusted Van Elteren statistic stratified by typical dose and typical dose plus 2 mg. If the primary contrast was found to be statistically significant, non-parametric ANCOVA was used to compare apomorphine and apomorphine + 2 against pooled placebo. If placebo and placebo + 2 were significantly different, additional analyses were done to compare apomorphine and placebo at each dosing scheme.

For the two secondary outcomes in APO 302 (change in dyskinesia assessment and WSST score at each time point), a non-parametric ANCOVA was used compare the pooled apomorphine and pooled placebo groups. The time to response was analyzed using the Wilcoxon rank sum test, with an imputed score of 40 minutes for patients if the time of onset of relief could not be documented (essentially akin to a “worst-case” scenario approach).

Sample size calculations for all three trials were based on the primary outcome: the mean change in UPDRS motor score from pre-dose to 20 minutes post-dose. In the APO 202 trial, there was a 2:1 ratio of apomorphine to placebo assignment. By estimating post-dose UPDRS-III motor scores (mean ± standard error) of 27.0 ± 12.0 points and 10.0 ± 12.0 points (no rationale provided) for placebo-treated and apomorphine-treated patients, respectively, it was calculated that eight patients in the placebo group and 16 patients in the apomorphine group provided 87% power to detect a difference of 17 points in the mean UPDRS motor score between the two groups at a 5% level of significance. A 10% to 20% dropout rate was expected in the trial. For APO 301, the estimated changes in UPDRS-III motor scores (mean ± standard deviation) were −0.11 ± 5.74 points and −23.85 ± 5.74 points for placebo and apomorphine, respectively. Assuming a dropout rate of 25% and a 5% level of significance, a sample size of 12 patients in each group provided > 99% power to detect a difference of 23.74 points in the change in mean UPDRS-III score. Based on the results of the APO 202 and APO 301 trials, estimated changes in UPDRS-III scores (mean ± standard deviation) of −5 ± 14 points for placebo and 20 ± 14 points for apomorphine were used for the sample size calculation in APO 302. It was calculated that with a 5% level of significance, 20 patients receiving placebo and 40 patients receiving apomorphine were adequate to provide 97% power to detect a difference of 15 points in the change in UPDRS motor score.

Methods for missing data imputation varied by study protocol and outcome variable. In APO 301 and APO 302, patients who did not self-declare an onset of symptom relief following treatment had their data for time to response imputed as 60 minutes and 40 minutes, respectively (maximum observation time). Missing data for UPDRS in APO 302 were imputed using the last observation carried forward method. No other forms of missing data imputation were done. The primary end point in APO 301 and APO 302 was analyzed in both the ITT and per-protocol (PP) populations. Finally, all statistical tests were two-sided with a 0.05 level of significance for efficacy end points.

Analysis Populations

The definitions for analysis set varied between the trials owing to the differences in trial design. In the APO 202 trial, the safety and ITT sets were the same and included all patients who were randomized and received at least one dose of the assigned treatment. The efficacy analyses for the primary objective of the trial — therapeutic response to subcutaneous apomorphine during induced "off" state in the in-patient phase — were done using this ITT set. Patients who continued through the in-patient phase and returned for at least one visit during the outpatient phase were used to analyze the secondary objective of the trial — effectiveness of chronic administration of subcutaneous apomorphine in aborting "off" episodes and total "off" time.

In the APO 301 trial, the ITT and safety populations included all patients who were randomized and received at least one dose of test medication. The PP population consisted of all randomized patients who completed both doses of test medication over two separate crossover visits. In the APO 302 trial, both the ITT and safety populations included all randomized participants who received either apomorphine or placebo on the treatment day visit. The PP population included the randomized groups of patients who received their assigned treatment and completed the study without any major protocol violation.

Patient Disposition

The total numbers of patients enrolled in the APO 202, APO 301, and APO 302 trials were 32, 17, and 62, respectively. All the patients enrolled in the three trials were randomized and received at least one apomorphine or placebo dose. Four patients discontinued the study in APO 202 compared with one and two in APO 301 and 302, respectively; all discontinuations were a result of AEs, lack of treatment effect, or other causes. The majority of the patients (> 84% to 100% across trial groups) completed the double-blind phase of the trials, and the dropout rates did not differ between groups. Details about patient disposition are provided in Table 6.

Table 6: Patient Disposition

	Study APO 202		Study APO 301		Study APO 302			
	APO	PLB	APO/PLB	PLB/APO	APO	APO + 0.2 mL	PLB	PLB + 0.2 mL
Enrolled, N	32[a]		17		35		27	
Randomized, N (%)	20 (100)	9 (100)	8 (100)	9 (100)	19 (100)	16 (100)	13 (100)	14 (100)
Discontinued in IP phase, N (%)	1 (5)	1 (11)	NA	NA	NA	NA	NA	NA
Adverse event	1 (5)	0	NA	NA	NA	NA	NA	NA
Lack of effect	0	1	NA	NA	NA	NA	NA	NA
Entered OP phase	19 (95)	8	NA	NA	NA	NA	NA	NA
Discontinued OP phase, N (%)	2 (10)	0	NA	NA	NA	NA	NA	NA
Adverse event	1 (5)	0	NA	NA	NA	NA	NA	NA
Schedule conflict	1 (5)	0	NA	NA	NA	NA	NA	NA
Total discontinuation, N (%)	3 (15)	1 (11)	0	1	0	0	2 (15.4)	0

	Study APO 202		Study APO 301		Study APO 302			
	APO	PLB	APO/PLB	PLB/APO	APO	APO + 0.2 mL	PLB	PLB + 0.2 mL
Adverse event	2 (10)	0	0	0	0	0	0	0
Lack of effect	0	1 (11)	0	0	0	0	2 (15.4)	0
Other	1(5)		0	1 (11)	0	0	0	0
Completed the study	17 (85)	8 (89)	8 (100)	8 (89)	19 (100)	16 (100)	11 (84.6)	14 (100)
ITT, N (%)	20 (100)	9 (100)	8 (100)	9 (100)	19 (100)	16 (100)	13 (100)	14 (100)
PP, N	NA	NA	8 (100)	8 (89)	18 (95)	16 (100)	13 (100)	14 (100)
Safety, N (%)	20 (100)	9 (100)	8 (100)	9 (100)	19 (100)	16 (100)	13 (100)	14 (100)

APO = apomorphine; CSR = Clinical Study Report; DB = double blind; IP = in-patient; ITT = intention-to-treat; NA = not applicable; OP = outpatient; PLB = placebo; PP = per-protocol.

[a] In Study 202, 3 patients were not randomized (2 failed levodopa test, 1 patient dropped out).

Source: Apo 202,[16] Study 202 CSR,[1] Study 301 CSR,[2] APO 302,[17] Study 302 CSR.[3]

Exposure to Study Treatments

The mean duration of exposure in the APO 202 trial was similar in both treatment groups, at 26. 1 days (apomorphine group) and 26.2 days (placebo group) (range, 1 to 30 days). During the in-patient phase, TED or maximum dose (if TED was not achieved) was achieved for three, seven, five, three, and two patients at 0.2 mL, 0.4 mL, 0.6 mL, 0.8 mL, and 1.0 mL per dose, respectively. Most patients in the placebo group were titrated to the maximum 1.0 mL (10 mg) dose. The mean apomorphine dose that resulted in a TED to levodopa was 5.4 mg during the in-patient phase. During the outpatient phase, further dose adjustments were done, with a mean 5.8 mg per dose, and an average 2.5 (maximum 5) injections were administered per day in the apomorphine-treated group as recorded in outpatient diaries. Patients in the APO 301 and APO 302 trials were exposed to apomorphine treatment for an average of 2.5 years (maximum 5) and 1.2 years (maximum 2.4) before enrolment, respectively, with an average of two injections/day in the week preceding the study. One dose of apomorphine or volume-matched placebo was given to all patients during the entire course of the two studies, which was based on the patient's usual subcutaneous apomorphine regimen. Patients in the apomorphine + 2 and placebo + 2 groups within the APO 302 trial received an additional 0.2 mL (2 mg) dose on top of their typically effective dose. The mean daily typically effective doses in APO 301 and APO 302 were 3.91 mg per bolus (range, 2 mg/bolus to 10 mg/bolus) and 3.82 mg per dose (range, 1.5 mg/dose to 10.0 mg/dose), respectively. The dose-titration period in the APO 202 trial and full treatment courses in both the APO 301 and APO 302 trials were conducted in strict in-patient conditions, where 100% compliance was ensured with recorded injection times corroborated by counts of used ampoules. In the outpatient phase of the APO 202 trial, however, per cent compliance was not possible to define since dosing decisions were left to the patients. Details about exposure in the placebo-controlled trials are provided in Table 7 and Table 8.

Table 7: Exposure to Study Treatment in APO 202

	APO 202	
Dosage	APO (N = 20)	PLB (N = 9)

	APO 202	
Dosage	**APO (N = 20)**	**PLB (N = 9)**
In-Patient Phase		
Dose level, mg (mL)[a]		
2 (0.2)	3	0
4 (0.4)	7	0
6 (0.6)	5	1
8 (0.8)	3	0
10 (1.0)	2	8
Mean TED, mg (SE)	5.4 (0.5)	5.4 (0.05)
Outpatient Phase		
Mean TED, mg (SE)	5.8 (NR)	NA
Mean number of injections/day, SE	2.5 (0.2)	2.3 (0.4)
Mean total daily dose, mg	10.6	18.0
Mean duration of treatment, days (range)	26.1 (1 to 30)	26.2 (1 to 30)
Number of days on treatment	APO (N = 17), n	PLB (N = 8), n
30	5	–
≥ 28	35	22
≥ 25	75	45
≥ 21	85	89
≥ 5	90	89
≥ 0	95	89
Mean injections per day, n	APO (N = 17), n (%)[b]	PLB (N = 8), n (%)[b]
> 3	5 (29)	2 (25)
2 to 3	6 (35)	0 (0)
1 to 2	5 (29)	4 (50)
0 to 1	1 (6)	2 (25)
Total daily dose, mg/day	APO (N = 17), n (%)[b]	PLB (N = 8), n (%)[b]
≥ 30	1 (5.9)	1 (12.5)
≥ 20 to < 30	2 (11.8)	1 (12.5)
≥ 10 to < 20	3 (17.6)	4 (50)
< 10	11 (64.7)	2 (25)

APO = apomorphine; PLB = placebo; SE = standard error; TED = therapeutically effective dose.

[a] Indicates highest dose received which can be either the TED, if achieved, or the maximum dose received.

[b] For those who completed week 4 treatment.

Source: Study 202 Clinical Study Report,[1] Health Canada Reviewers Report.[4]

Table 8: Exposure to Study Treatment in APO 301 and APO 302

	APO 301	APO 302
Dose	**APO/PLB (N = 17), n (%)**	**Pooled APO/PLB (N = 62), n (%)**
Dose Level, mg (mL)		
2 (0.2)	2 (11.7)	8 (12.9)

	APO 301	APO 302
Dose	APO/PLB (N = 17), n (%)	Pooled APO/PLB (N = 62), n (%)
3 (0.3)	9 (52.9)	6 (9.6)
3.5 (0.35)	–	2 (3.2)
4 (0.4)	2 (11.7)	13 (20.9)
4.5 (0.45)	1(5.9)	1 (1.6)
5 (0.5)	1(5.9)	11(17.7)
6 (0.6)	–	13 (20.9)
7 (0.7)	–	2 (3.2)
7.5 (0.75)	–	1 (1.6)
8 (0.8)	1(5.9)	2 (3.2)
9 (0.9)	–	1 (1.6)
10 (1.0)	1(5.9)	2 (3.2)
Mean Daily APO Dose Per Bolus/Injection, (SE) (Range)	3.9 (0.5)	3.8 (0.2) (1.5/dose to 10.0/dose)
Mean Duration of APO Dose, Years	2.5	1.2

APO = apomorphine; CSR = Clinical Study Report; PLB = placebo; SE = standard error.

Note: Pooled APO includes patients who received APO in their typically effective dose or typically effective dose + 0.2 mL; pooled PLB includes patients who received placebo volume-matched to APO or placebo + 0.2 mL.

Source: Study 301 CSR,[2] APO 302,[17] Study 302 CSR.[3]

Critical Appraisal

Internal Validity

All three included trials were randomized, double-blind, and placebo-controlled in nature, and all were phase III except for APO 202, which was a phase II trial. Patients in the APO 202 trial were randomized by site in blocks of three using a computer program. Patients in the APO 301 trial were randomized to receive either apomorphine or placebo in a predetermined crossover fashion on two alternate days, or either apomorphine or placebo at their standard dose (or 0.2 mL extra) in a parallel manner in APO 302. The method of randomization for both APO 301 and APO 302 was unclear. In all three trials, apomorphine and pH-matched placebo were packaged in identical ampoules, concealing the assignment of study medications. In addition, the investigators and support staff did not have access to blinding assignments until after patients completed the study. However, it is may have been difficult to functionally maintain blinding of treatments due to the obvious and apparent change in PD symptoms and potential AEs from treatment. The extent to which the results were biased by inadvertent unblinding would depend on how objectively the outcomes were measured. Subjective outcomes based on patient diaries (e.g., perceived time to onset of relief) and AE reporting may have been prone to bias. Scale outcomes such as UPDRS, HTT score, DRS score, and WSST score may also have been biased as outcome assessors may have deduced the treatment allocation based on patients' PD symptoms, especially when the scale elements were closely spaced (e.g., slight versus mild as opposed to slight versus severe). Patients in APO 301 and APO 302 had been previously exposed to apomorphine treatment and would have been more likely to recognize a response or lack of response to apomorphine. There may have been the potential for overestimation of treatment effects if a disproportional percentage of patients in each treatment group were

able to ascertain their treatment group assignment, particularly for the outcomes that were vulnerable to biased reporting resulting from potential unblinding. Sensitivity analyses using different outcome scores may have helped inform the impact of this potential bias; however, no such sensitivity analyses were done. However, the clinical expert consulted for this review suggested that any such bias was unlikely to explain the reported large treatment effect.

A 100% treatment adherence was assured in APO 301 and APO 302 and in the dose-titration period of APO 202 due to the strict, in-patient administration of treatment and measurement of primary end point data. Patients or their caregivers were trained before the outpatient phase to administer the treatment as needed, but a pre-specified compliance definition was not in place.

In terms of the outcome measures used in the included studies, the UPDRS is a commonly used tool to measure severity of PD and has been validated extensively (refer to Appendix 5 for details). However, evidence on psychometric properties for the DRS, HTT, and (modified) WSST is sparse and it is uncertain how commonly these scales are used in clinical practice. Therefore, the appropriateness of using these tests is also uncertain. Patient-reported outcomes through self-report or daily diaries were used to measure the frequency, duration, and latency of “off” episodes as well as numbers of injections and success rate of injections in aborting “off” events. Due to the subjective nature of these outcomes and the limited evidence of the reliability of the measure, the treatment effects could potentially be inflated resulting from biased reporting, particularly if blinding was compromised. According to the Health Canada Reviewers Report, the APO 202 trial that collected information on “off” episodes did not place enough emphasis on daily “on” time, and it was noted that aborting “off” time may be relevant only if patients experienced an accompanied increase in “on” time.

The primary efficacy end point in all trials — change in UPDRS motor score at or around 20 minutes post-dose — and all continuous secondary efficacy end points were analyzed using ANCOVA or the non-parametric Wilcoxon rank sum test if assumptions of normality were not met. In the APO 301 trial, repeated-measures ANCOVA was used to account for multiple measures of the efficacy variables. In addition, the effect of sequence, period, and treatment by period interaction were assessed due to the crossover design of the study. In the APO 302 trial, the pooled placebo group was used for analysis comparison with the pooled apomorphine group after no difference was found between the placebo and placebo + 2 group, and the non-parametric analyses using the Van Elteren statistic confirmed the results. Statistical analyses were conducted in both the ITT and PP populations in APO 301 and APO 302 to assess the effect of treatment withdrawal or non-compliance; however, the results did not vary significantly in the PP population. In the APO 202 trial, separate analyses in the ITT and PP populations were not done. Efficacy variables for the primary objective were analyzed in the ITT/safety population, and efficacy variables for the secondary objective were analyzed in the secondary efficacy population without imputing missing data for the patients who did not enter the outpatient phase following the in-patient phase. The ITT numbers used in the primary efficacy analyses for all trials were identical to the true ITT definition.[27] Attrition rates were absent or sufficiently low in all trials; therefore the likelihood of missing data impacting the outcomes was reduced. A number of methods to impute missing data were in place and varied by study protocol and outcome variable.

None of the secondary end points was controlled for multiple statistical testing, and results from these outcome analyses should be considered exploratory in nature. Furthermore,

since the sample size calculation was done based on the primary efficacy outcome, results from the secondary analyses may be underpowered. No rationale was provided for the estimated UPDRS scores chosen in APO 202 and APO 301 sample size calculation.

External Validity

The three trials were conducted among patients with advanced PD (stages 2 to 4 on the H&Y scale for PD severity) who experienced refractory motor fluctuations and "off" episodes despite optimized oral anti-PD medications. Therefore, the results are largely generalizable to patients with these features. None of the trials was conducted in Canada, and it is uncertain if the differences between patients in Canada and the study populations would influence the generalizability of the results. Patients with significant psychological and clinical comorbidities (including orthostatic hypotension) were excluded from the studies. However, if a sizable proportion of PD patients also suffer from these conditions due to old age (such as dementia, psychoses, and cardiovascular diseases), the results may not be generalizable to those patients. In terms of demographics, the majority of the patients were Caucasian, and more male patients than female patients were included in the trial. This preponderance of PD in Caucasians and males is mostly consistent with the literature as well as the clinical expert's experience. A varied range of UPDRS-III scores was seen at baseline across the trials, depending on whether assessments were done during "on" or "off" states. However, the mean pre-dose "off" state UPDRS-III score was similar across trials, ranging from 39 to 42.

In the APO 202 trial, patients were given study medications after inducing "off" events during the in-patient phase by withholding their usual anti-PD medications overnight to represent a worst-case scenario, with the expectation that any treatment showing effectiveness under these conditions would likely be effective for the spontaneous "off" events ("end-of-dose wearing off" or unpredictable "on/off"). Patients in the outpatient phase administered the study medication up to five times per day in response to spontaneous "off" events in addition to concomitant anti-PD medications, which was more closely reflective of the real-world use of apomorphine. Furthermore, patients in the APO 301 and APO 302 trial administered the study medication at least one hour after their regular anti-PD medication, after an "off" episode occurred. This represents more closely the "end-of-dose wearing off" episodes that patients may experience. Therefore, all types of "off" episodes have been evaluated across the studies for apomorphine effectiveness. The clinical expert consulted for this review indicated that the efficacy of apomorphine should be consistent regardless of the type of "off" episode experienced by the patient.

The mean dose across all trials was within the manufacturer-recommended maximum dose of 6 mg per injection. Most patients received no more than three doses per day, which was also within the maximum recommended daily dose of 2 mL (2 mg). The range of mean doses varied between the studies. In APO 202, the mean TED was 5.4 mg and 5.8 mg per dose during the in-patient and outpatient phases, respectively. In APO 301 and APO 302, the typically effective mean dose before study enrolment was 3.9 mg/bolus and 3.8 mg/dose, respectively. In the APO 302 trial, however, the dosing differed on treatment day, with the apomorphine group receiving a mean dose of 4.6 mg/dose and the apomorphine + 2 group a mean dose of 5.8 mg/dose. It should be noted that the mean doses were close to the maximum recommended dose of 6 mg, and therefore some patients are expected to exceed this limit. The clinical expert indicated that an individual dose of more than 6 mg is not common. The median dose per injection was not reported in any of the trials; therefore it is uncertain how many patients received a dose higher than the recommended limit. Even

though the Health Canada–approved product monograph indicated there was no increase in treatment effect seen above 6 mg per injection, the uncertainty that is associated with an improvement in outcomes resulting from individual doses above 6 mg in some patients should be acknowledged.

Long-term AEs of apomorphine may not be apparent due to the short follow-up duration (particularly in APO 301 and APO 302, which were completed within two visits), and the sample sizes in all three trials were not calculated to capture AEs. However, longer-term safety data were available from the one-year APO 401 trial and the six-month substudy APO 303 coinciding within it
(Appendix 6).

Efficacy

Only those efficacy outcomes identified in the review protocol (Table 3) are reported below. Unless otherwise specified, all results discussed below were obtained from an analysis of the ITT population of the studies. See Appendix 4 for additional efficacy data.

Unified Parkinson's Disease Rating Scale, Part III

Details pertaining to UPDRS-III outcomes in the three placebo-controlled trials are provided in Table 9 to Table 11.

In the APO 202 trial, there was no statistically significant difference between the two groups in their UPDRS-III score from "off" to "on" state following the dopaminergic challenge test. However, the change in UPDRS motor score from baseline (i.e., "off" state) to "on" state was statistically significantly greater for patients receiving apomorphine at the TED compared with the patients in the placebo group ($P < 0.0001$). No between-group differences in change scores for the UPDRS from baseline to "on" state were reported.

Response ratio (% change in raw score from baseline on study medication / % change in raw score from baseline on levodopa) for the UPDRS-III score showed consistent findings (Appendix 4, Table 22), where the response ratio with apomorphine was statistically significantly greater than with placebo. The apomorphine group also had a response ratio close to 1.0, indicating that the response elicited by apomorphine was similar to the response to levodopa.

In the APO 301 trial, patients receiving apomorphine had a statistically significantly greater reduction in UPDRS-III score from baseline compared with the placebo group at all three time points. The score was reduced by about 36% at 10 minutes, about 47% at 20 minutes, and about 30% at 60 minutes compared with pre-dose score. Since no statistically significant treatment by period interaction was found from the analysis of sequence effect (shown in Table 23 in Appendix 4), analysis of day 1 data in parallel groups was not necessary to report.

In the APO 302 trial, the primary contrast was between the pooled apomorphine and pooled placebo groups. Since there was no significant difference between the placebo and placebo + 2 groups in mean UPDRS score at 20 minutes post-dose ($P = 0.77$), data from the pooled placebo group were used for comparative analyses. There were statistically significantly greater reductions of more than 31% and 35% in UPDRS motor scores in the pooled apomorphine group compared with the pooled placebo group at 10 and 20 minutes post-dose, respectively, but the reduction was not statistically significant at 90 minutes post-dose.

The results of the non-parametric analysis of the primary efficacy end point confirmed the results of the parametric analysis (data not shown). In both APO 301 and APO 302, the results were consistent at all time points in analyzing the PP populations (data not shown). The mean changes in UPDRS-III motor score in apomorphine-treated patients in all three trials exceeded the MCIDs reported across these studies (−5 points to −6.5 points), irrespective of time points and statistical significance.

Table 9: Change in UPDRS-III Score from "Off" to "On" State in APO 202

Study Phase	APO (N = 20)	PLB (N = 9)	*P* Value[a]
Dopaminergic Challenge, Mean (SE)			
"Off"-state score	41.80 (2.6)	39.89 (2.9)	
"On"-state score	15.20 (2.0)	17.30 (3.0)	
Score change	−26.60 (2.0)	−22.56 (2.7)	0.30
% change	−64.67 (3.7)	−57.84 (6.2)	0.27
Blinded Test Medication, Mean (SE)			
"Off"-state score	39.65 (2.0)	36.33 (2.3)	
"On"-state score	15.80 (2.4)	36.30 (2.3)	
Score change	−23.85 (1.9)	−0.11 (1.3)	< 0.0001
% change	−61.74 (4.4)	−1.04 (3.7)	< 0.0001

ANCOVA = analysis of covariance; APO = apomorphine; PLB = placebo; SE = standard error; UPDRS = Unified Parkinson's Disease Rating Scale.

[a] *P* values were derived from an ANCOVA with change or % change as dependent variable and "off"-state event score and treatment as independent variables.

Source: APO 202,[16] APO 202 Clinical Study Report.[1]

Table 10: Change in UPDRS-III Score From Pre-Dose in APO 301

Outcome Parameter	APO (N = 17)	PLB (N = 17)	*P* Value[a]
Time-Course, Mean (SE)			
Pre-dose score	41.3 (2.5)	40.1 (2.2)	
10 minutes post-dose	25.9 (3.4)	37.4 (2.9)	
Change from pre-dose	−15.4 (3.7)	−2.7 (2.0)	0.008
% change from pre-dose	−35.9 (7.4)	−6.7 (5.0)	0.004
20 minutes post-dose[b]	21.3 (3.5)	37.1 (2.3)	
Change from pre-dose	−20.0 (3.6)	−3.0 (2.2)	< 0.0001
% change from pre-dose	−47.4 (8.6)	−5.9 (5.0)	0.0001
60 minutes post-dose	28.7 (3.3)	39.8 (2.1)	
Change from pre-dose	−12.6 (2.9)	−0.4 (1.3)	0.0009
% change from pre-dose	−30.2 (6.8)	0.1 (3.4)	0.001

ANCOVA = analysis of covariance; APO = apomorphine; PLB = placebo; SE = standard error; UPDRS = Unified Parkinson's Disease Rating Scale.

[a] Repeated-measures ANCOVA with terms sequence, subject within sequence, pre-dose score, treatment, and period.

[b] Primary outcome measure.

Source: APO 301 Clinical Study Report.[2]

Table 11: Change in UPDRS-III Score from Baseline in APO 302

Outcome Parameter	Pooled APO (N = 35)	Pooled PLB (N = 27)	Treatment Difference (Pooled APO − Pooled PLB), Estimate (SE)	*P* Value
Time-Course, Mean (SE)				
Pre-dose score	42.0 (1.8)	40.6 (3.4)		
10 minutes post-dose	22.1 (2.3)	35.0 (4.2)		
Change from pre-dose	−19.9 (1.8)	−5.6 (1.6)	−14.6 (2.4)	< 0.0001
% change from pre-dose	−48.9 (4 .4)	−19.3 (5.4)	−31.1 (6.2)	< 0.0001
20 minutes post-dose[a]	17.8 (1.9)	33.3 (4.4)		
Change from pre-dose	−24.2 (1.7)	−7.4 (1.8)	−16.9 (2.5)	< 0.0001
% change from pre-dose	−58.7 (3.8)	−24.1 (5.6)	−35.6 (6.2)	< 0.0001
90 minutes post-dose	36.7 (2.6)	35.7 (4.3)		
Change from pre-dose	−5.2 (1.8)	−4.9 (2.0)	−0.5 (2.8)	0.86
% change from pre-dose	−13.6 (4.3)	−15.0 (5.1)	0.8 (6.7)	0.90

ANCOVA = analysis of covariance; APO = apomorphine; LOCF = last observation carried forward; PLB = placebo; SE = standard error; UPDRS = Unified Parkinson's Disease Rating Scale.
Note: *P* values are based on estimate statement in ANCOVA with the terms pre-dose score and treatment, comparing least square means. Missing values for 10, 20, and 90 minutes were imputed using LOCF.
Pooled APO includes patients who received APO in their typically effective dose or typically effective dose + 0.2 mL; pooled PLB includes patients who received placebo volume-matched to APO or placebo + 0.2 mL.
[a] Primary outcome measure.
Source: Study 302 Clinical Study Report.[3]

Dyskinesia Rating Scale

Patients in the APO 202 trial had no statistically significant difference in their dyskinesia score following dopaminergic challenge between the two treatment groups. Following apomorphine injection, the dyskinesia score in the apomorphine-treated group was higher than that in the placebo group (*P* = 0.001) and was similar to that found with levodopa treatment. Results from the APO 301 trial showed increased severity of dyskinesia in the apomorphine-treated patients compared with the placebo patients, a difference that was statistically significant at 10 minutes post-dose (*P* = 0.02), nonsignificant at 20 minutes (*P* = 0.05), and nonsignificant at 60 minutes. Similarly, patients in the APO 302 trial who received apomorphine had statistically significant increases in dyskinesia compared with the placebo group at 10 minutes (*P* = 0.002) and 20 minutes (*P* < 0.0001) post-dose but not at 90 minutes post-dose (*P* = 0.25). Similar results were found using the PP population in APO 301 and APO 302 (data not shown). The severity of dyskinesia was scored using the DRS. There is no reported MCID value for scores measured using DRS. Details about DRS scores are provided in Table 12 and Table 13.

Table 12: Change in Dyskinesia Score in APO 202

Study Phase	APO (N = 20)	PLB (N = 9)	*P* Value[a]
Dopaminergic Challenge			
"Off"-state score, median	0	0	
"On"-state score, median (Q3 to Q1)	1 (0.5)	1 (1)	
Score change	1 (0.5)	1 (2)	0.92
Blinded Test Medication			
"Off"-state score, median	0	0	
"On"-state score, median (Q3 to Q1)	1 (1.5)	0	
Score change	1 (1.5)	0	0.001
Outpatient Treatment Phase			
Severity of dyskinesia, score[b]	1.6	1.2	0.81

APO = apomorphine; PLB = placebo; Q3 to Q1 = difference between the 75th and 25th percentile.

[a] *P* value derived from Wilcoxon rank sum test with change as dependent variable and treatment as independent variable.

[b] Dyskinesia severity score: 0 = absent, 1 = mild, 2 = impaired voluntary movements, 3 = intense dyskinesia greatly limiting normal activities, 4 = violent dyskinesia.

Source: APO 202,[16] APO 202 Clinical Study Report.[1]

Table 13: Change in Dyskinesia Score in APO 301 and APO 302

	APO 301		APO 302		
Outcome Parameter	APO (N = 17)	PLB (N = 17)	Pooled APO (N = 35)	Pooled PLB (N = 27)	*P* Value
Time-Course, Median (Min, Max)					
Pre-dose score	NR	NR	0	0	
10 minutes post-dose	0 (0, 2)	0 (−3, 0)	0	0	0.02[a]
% change from pre-dose			0.0 (−1, 2)	0.0 (−1, 2)	0.002[b]
20 minutes post-dose	1 (−3, 3)	0 (0, 0)	1	0	0.05[a]
% change from pre-dose			0.0 (−1, 2)	0.0 (−1, 0)	< 0.0001[b]
60[a] or 90[b] minutes post-dose	0 (−3, 3)	0 (−3, 0)	0	0	0.11[a]
% change from pre-dose			0.0 (0, 1)	0.0 (−1, 2)	0.25[b]

ANCOVA = analysis of covariance; APO = apomorphine; CSR = Clinical Study Report; max = maximum; min = minimum; NR = not reported; PLB = placebo.

Note: Pooled APO includes patients who received APO in their typically effective dose or typically effective dose + 0.2 mL; pooled PLB includes patients who received placebo volume-matched to APO or placebo + 0.2 mL.

[a] *P* values derived using Wilcoxon signed rank test in APO 301 comparing pooled APO and pooled PLB.

[b] *P* values based on non-parametric ANCOVA in APO 302 comparing pooled APO and pooled PLB.

Source: APO 301 CSR,[2] APO 302 CSR.[3]

Hand-Tapping Test

The HTT score was reported only for APO 202 and was analyzed using ANCOVA. It was found that patients treated with apomorphine had a higher score in the HTT during their "on" state compared with their "off" state, and the improvement in raw score was statistically significant compared with placebo (*P* = 0.0008). The per cent change in HTT score from baseline was numerically greater with apomorphine compared with placebo. Details about HTT scores are provided in Table 14.

Table 14: Change in Hand-Tapping Test Score in APO 202

Study Phase	APO (N = 19)	PLB (N = 9)	*P* Value[a]
Dopaminergic Challenge, Mean (SE)			
"Off"-state score	236 (13)	216 (26)	
"On"-state score	356 (21)	340 (35)	
Score change	120 (9.2)	124 (28)	0.98
% change	55 (9.2)	70 (23)	0.68
Blinded Test Medication, Mean (SE)			
"Off"-state score	265 (22)	255 (16)	
"On"-state score	374 (24)	243 (19)	
Score change	109 (23)	−12 (14)	0.0008
% change	88 (51)	−4 (5.3)	0.10

ANCOVA = analysis of covariance; APO = apomorphine; HTT = hand-tapping test; PLB = placebo; SE = standard error; UPDRS = Unified Parkinson's Disease Rating Scale; WSST = Webster step-seconds test.

Note: N = 20 for all parameters during the dopaminergic challenge phase, but N = 19 for the HTT scores during the blinded treatment phase (1 patient discontinued due to nausea/vomiting after 0.6 mL; UPDRS was assessed, but HTT and WSST scores were not).

[a] *P* values derived from ANCOVA with change as dependent variable, and "off"-state event score and treatment as independent variables

Source: APO 202,[16] APO 202 Clinical Study Report.[1]

Webster Step-Seconds Test

During the dopaminergic challenge phase in the APO 202 trial, levodopa treatment led to a median decrease of 50% to 80% in WSST score from "off" to "on" state in both treatment groups. During the double-blind treatment phase, injection of subcutaneous apomorphine led to a statistically significant median decrease of 65% in WSST scores from "off" state to "on" state without any concomitant change in the placebo group ($P < 0.001$). In the APO 302 trial, the time-course of WSST score over 40 minutes following apomorphine or placebo administration was determined. In the pooled apomorphine group, the median WSST score decreased gradually across almost all time points, in contrast with the pooled placebo group. The improvement in median WSST score from pre-dose was statistically significant at all time points from 7.5 minutes onward for the pooled apomorphine group in comparison with the pooled placebo group. Identical findings were reported using the PP population (data not shown). Even though an MCID was not available for WSST score, it was noted that treatment with apomorphine resulted in a median score of 128 during the "on" state in APO 202 and 120 step-seconds by 40 minutes in the APO 302 trial, which were close to the upper limit of the range (50 to 100) typically found in people without PD.[28] Details about WSST scores are provided in Table 15 and Table 16.

Table 15: Change in Webster Step-Seconds Test Score in APO 202

Study Phase	APO (N = 20)	PLB (N = 9)	*P* Value[a]
Dopaminergic Challenge, Median (Q3 to Q1)			
"Off"-state score	431 (7,754)	504 (4,940)	
"On"-state score	124 (92)	98 (59)	
Score change	−336 (7,168)	−204 (5,028)	0.45
% change	−80 (42)	−50 (58)	
Blinded Test Medication, Median (Q3 to Q1)			
"Off"-state score	552 (9,820)	273 (9,734)	
"On"-state score	128 (97)	323 (9,804)	
Score change	−402 (9,701)	0 (29)	< 0.001
% change	−65 (65)	0 (14)	

APO = apomorphine; PLB = placebo; Q3 to Q1 = difference between the 75th and 25th percentile

[a] *P* values derived from Wilcoxon rank sum test with change as dependent variable and treatment as independent variable.

Source: Apo 202.[16]

Table 16: Change in Webster Step-Seconds Test Score in APO 302

Time From Pre-Dose (Minutes)	Pooled APO (N = 35)		Pooled PLB (N = 27)		
	Median	Median Change From Pre-Dose (Min, Max)	Median	Median Change From Pre-Dose (Min, Max)	*P* Value
0	683.0		760.0		
2.5	360.0	−36.5 (−9,774, 7,799)	671.5	−36.5 (−1,644, 9,299)	0.35
5	340.0	−50.0 (−9,759, 9,257)	672.0	−28.0 (−1,042, 9,299)	0.28
7.5	195.0	−269.5 (−9,899, 9,257)	891. 0	−58.0 (−1,480, 9,299)	0.02
10	168.0	−400.5 (−9,918, 90)	432.0	−78.0 (−8,289, 9,299)	0.005
15	130.0	−426.5 (−9,919, 0)	384.0	−66.0 (−9,719 to 9,299)	0.0005
20	143.0	−462.5 (−9,927, 8)	378.0	−39.0 (−9,819, 9,299)	< 0.0001
40[a]	120.0	−445.0 (−9,927, 0)	402.5	−62.5 (−9,855, 9,299)	0.0004

ANCOVA = analysis of covariance; APO = apomorphine; max = maximum; min = minimum; PLB = placebo.

Note: *P* values are based on non-parametric ANCOVA.

Pooled APO includes patients who received APO in their typically effective dose or typically effective dose + 0.2 mL; pooled PLB includes patients who received PLB volume-matched to APO or PLB + 0.2 mL.

[a] 34 patients in the pooled APO group and 26 patients in the pooled PLB group completed the 40-minute test; 1 patient from each group discontinued.

Source: APO 302 Clinical Study Report.[3]

Duration of "Off" Episodes

There was a decrease in mean (−1.7 hours) and median (−2.0 hours) change in daily duration of "off" episodes post-baseline from baseline in the apomorphine-treated group compared with the placebo group; however, statistical significance was seen only for the non-parametric Wilcoxon rank sum test. This parameter was not reported in the APO 301 and APO 302 trials. The mean decrease in "off" time in APO 202 was close to the upper bound of the MCID range that has been reported in previous studies (i.e., 1 hour to 1.8 hours). Details about daily durations of "off" time are provided in Table 17.

Table 17: Change in Average Daily Length of Time (Hours) of "Off" Events in APO 202

Treatment	Baseline	Post-Baseline	Mean Change From Baseline	Median Change From Baseline	*P* Value[a]	*P* Value[b]
APO (N = 18)	5.8	4.1	−1. 7	−2.0	0.08	0.01
PLB (N = 8)	6.5	6.5	0.0	−0.0		

ANCOVA = analysis of covariance; APO = apomorphine; PLB = placebo.

[a] *P* value for mean change derived from an ANCOVA model with change from baseline as dependent variable, and treatment and baseline value as independent variables.

[b] *P* value for median change derived from Wilcoxon rank sum test.

Source: APO 202,[16] APO 202 Clinical Study Report.[1]

Other Outcomes

Time to Response (Interval Between Injection and Declared Recovery)

In the APO 202 trial, during both the dopaminergic challenge phase and the blinded test medication administration phase, the average amount of time (minutes) from drug injection until patients demonstrated relief from "off" state was determined clinically, followed by administration of the motor exam. The time to UPDRS-III assessment was not statistically significantly different between the treatment groups in either phase. However, the average time to clinically determined "on" state following injection of medication was statistically significantly lower in the apomorphine group compared with the placebo group (*P* = 0.0005). Patients in both APO 301 and APO 302 were asked to self-declare the time of perceived relief from symptoms.

In the APO 301 trial, the median time to response was statistically significant in favour of apomorphine over placebo (15 versus 60 minutes, *P* = 0.01) using a non-parametric test, and the result in the PP population was identical (data not shown). However, further analysis conducted with actual onset of relief data showed 13 out of 17 patients reported relief on apomorphine treatment day and 4 out of 17 patients on placebo treatment day, suggesting that the median time of onset in the placebo group with imputed missing data was 60 minutes, because most patients could not declare an onset. When excluding those patients who did not explicitly declare a time of onset, a reanalysis of the mean time of onset of relief showed it to be slightly but not statistically significantly higher in the apomorphine group (13.3 minutes) compared with the placebo group (9.5 minutes).

In the APO 302 trial, three different methods were used to compare the subjective assessment of onset of relief between the pooled apomorphine and pooled placebo groups. Both the non-parametric Wilcoxon rank sum test and parametric ANOVA test results found no statistically significant difference in the two groups in median and mean time to onset of relief, respectively. Using the log-rank test to compare the mean time to onset of relief after accounting for censored observations, it was shown that the mean time to response was statistically significantly lower in the apomorphine group compared with the placebo group (7.2 minutes versus 11.4 minutes, *P* = 0.005). These results were consistent in the PP population. Of note, the average time to response in the apomorphine group of 7.2 minutes was close to the time point at which the WSST score (which was used to objectively measure onset of symptom relief) was first found to be statistically significantly different than in the placebo group (7.5 minutes). In the APO 202 trial, patients who did not demonstrate an onset of relief from symptoms were excluded from the analysis, whereas in the APO 301 and APO 302 trials, patients who failed to self-declare response within the time frame of the

test were imputed as 60 minutes and 40 minutes, respectively. Details about times to onset of symptom relief are provided in Table 18 and Table 19.

Table 18: Time (Minutes) to Response in APO 202

Study Phase/Parameter	APO (N = 20)	PLB (N = 9)	*P* Value[a]
Dopaminergic challenge: minutes from levodopa to time of UPDRS, mean (SE)	54 (5.7)	46 (8.0)	0.44
Blinded test medication: minutes from highest dose administration to time of UPDRS, mean (SE)	19 (1.5)	17 (1.7)	0.40
Average time (minutes) from injection of test medication to "on" state, mean (SE)	22.1 (2.44)[b]	44.8 (5.65)[c]	0.0005

ANOVA = analysis of variance; APO = apomorphine; PLB = placebo; SE = standard error; UPDRS = Unified Parkinson's Disease Rating Scale.

[a] *P* value calculated from an ANOVA model with treatment as independent variable.

[b] N = 18 for average time from injection to "on" state.

[c] N = 5 for average time from injection to "on" state.

Source: APO 202,[16] APO 202 Clinical Study Report.[1]

Table 19: Time (Minutes) to Response in APO 301 and APO 302

	APO 301			APO 302		
Outcome Parameter	APO (N = 17)	PLB (N = 17)	P Value	Pooled APO (N = 35)	Pooled PLB (N = 27)	*P* Value
Time to patient-declared relief, median (min, max)	15 (2, 60)	60 (9, 60)	0.01[a]	5 (2.5, 40)	7.5 (2.5, 40)	0.15[b]
Time to patient-declared relief, mean (SE)	13.3 (2.5)[c]	9.5 (0.3)[c]	0.07[c]	6.9 (0.79)	7.8 (1.51)	0.53[d]
Time to patient-declared relief, mean (SE), no. of censored subjects				7.2 (0.85), 1 censored	11.4 (1.53), 8 censored	0.005[e]

APO = apomorphine; CSR = Clinical Study Report; max = maximum; min = minimum; PLB = placebo; SE = standard error.

Note: Pooled APO includes patients who received APO in their typically effective dose or typically effective dose + 0.2 mL; pooled PLB includes patients who received placebo volume-matched to APO or placebo + 0.2 mL.

[a] *P* values based on Wilcoxon signed rank test; missing values set at 60 minutes if no relief reported.

[b] *P* value based on Wilcoxon rank sum test; missing values set at 40 minutes if no relief reported.

[c] Analysis excluding missing values; N = 13 for APO and N = 4 for PLB; *P* values based on repeated-measures ANOVA with terms sequence, subject within sequence, treatment, and period.

[d] *P* value based on ANOVA; missing values set at 40 minutes if no relief reported, with N = 34 for pooled APO and N = 19 for pooled PLB.

[e] *P* value based on log-rank test; missing values set at 40 minutes if no relief reported.

Source: APO 301 CSR,[2] APO 302 CSR.[3]

Frequency of "Off" Events

The frequency of "off" events was compared only in the APO 202 trial, during the outpatient phase and using patient-recorded daily diaries. The average number of "off" events per day did not change significantly between apomorphine-treated and placebo-treated patients (−0.1 versus −0.3, *P* = 0.44).

Proportion of Injections Declared to Have Aborted the "Off" Event

The proportion of injections resulting in aborted "off" states in patients was reported only in the outpatient phase of the APO 202 trial with the use of patient daily diaries. In the apomorphine group, a mean total of 63.7 injections were used per patient during the four-week period and a mean total of 61.1 "off" episodes were successfully aborted. Just greater than 95% of "off" states were aborted by apomorphine injections as opposed to 23% in the placebo group, which was statistically significantly different (*P* = 0.0001) with non-parametric analysis. It was also shown that the mean percentages of "off" events aborted by the first and last daily dose of apomorphine were not statistically significantly different (*P* = 0.15), indicating no treatment waning effect over the course of the study. Details about "off" events aborted by injections are provided in Table 20.

Table 20: "Off" Events Aborted by Injections in APO 202

Outpatient Diary Parameter	APO (N = 20)	PLB (N = 9)	*P* Value
"Off"-state events aborted per patient, % (SE)	95.2 (2.4)	23.1 (13)	0.0001[a]
Mean % of "off"-state events aborted (SE)			
First daily dose	96.5 (9.9)	ND	0.15[b]
Last daily dose	95.3 (12.7)	ND	

APO = apomorphine; ND = not done; PLB = placebo; SE = standard error.

[a] *P* value based on Wilcoxon rank sum test of individual averages.

[b] *P* value based on t-test comparing the % of "off" events aborted by the first daily dose with the % of "off" events aborted by the last daily dose.

Source: APO 202,[16] APO 202 Clinical Study Report.[1]

Harms

Adverse Events

The majority of the patients in the APO 202 trial (≥ 85%) experienced AEs at least once during the duration of the study. In contrast, only three AEs were registered by the patients receiving placebo in the APO 301 trial. In the APO 302 trial, more than one-third of the patients (40.3%) experienced at least one AE. Most of the AEs were of mild to moderate severity. Overall, the most AEs resulting from apomorphine treatment, in descending order of frequency, were injection site disorders, yawning, dyskinesia, somnolence, nausea, dizziness, and rhinorrhea. Of these, psychiatric disorders (including agitation, appetite stimulation, confusion, hallucination, insomnia, and somnolence) appeared more frequently in the apomorphine-treated patients compared with placebo-treated patients in the APO 202 trial. Patients treated with apomorphine in the APO 302 trial experienced yawning, somnolence, and dizziness more frequently compared with placebo (data not shown). Details about AEs are provided in Table 21.

Table 21: Treatment-Emergent Adverse Events

	APO 202		APO 301		APO 302	
AEs	APO (N = 20)	PLB (N = 9)	APO (N = 16)	PLB (N = 17)	Pooled APO (N = 35)	Pooled PLB (N = 27)
Any AE, n (%)	17 (85)	8 (89)	0 (0)	3 (17.6)	16 (45.7)	9 (33.3)
Injection site complaint/ reaction	9 (45)	5 (56)	0 (0)	2 (11.8)	0 (0)	1 (3. 7)
Yawning	8 (40)	0 (0)	0 (0)	0 (0)	8 (22.9)	2 (7.4)
Dyskinesia	7 (35)	1 (11)	0 (0)	0 (0)	1 (2.9)	1 (3.7)
Drowsiness or somnolence	7 (35)	0 (0)	0 (0)	0 (0)	6 (17.1)	0 (0)
Nausea	6 (30)	1 (11)	0 (0)	0 (0)	2 (5.7)	0 (0)
Dizziness or postural dizziness	4 (20)	0 (0)	0 (0)	0 (0)	4(11.4)	1 (3.7)
Rhinorrhea	4 (20)	0 (0)	0 (0)	0 (0)	3 (8.6)	0 (0)
Chest pain/ pressure or angina	3 (15)	1 (11)	0 (0)	0 (0)	1 (2. 9)	0 (0)
Cardiac arrhythmia					0 (0)	1 (3.7)
Hallucination or confusion	2 (10)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Edema/ swelling of extremities	2 (10)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Skin disorders	NR	NR	0 (0)	1 (5.9)	1 (2. 9)	0 (0)
Fall/ bruised ribs	NR	NR	0 (0)	0 (0)	0 (0)	0 (0)
Back pain	NR	NR	0 (0)	0 (0)	0 (0)	0 (0)

AE = adverse event; APO = apomorphine; CSR = Clinical Study Report; NR = not reported; PLB = placebo.

Note: Pooled APO includes patients who received APO in their typically effective dose or typically effective dose + 0.2 mL; pooled PLB includes patients who received placebo volume-matched to APO or placebo + 0.2 mL.

Source: APO 202,[16] APO 202 CSR,[1] APO 301 CSR,[2] APO 302,[17] APO 302 CSR.[3]

Serious Adverse Events

Only one SAE (chest pain, not due to myocardial infarction) was registered in a patient in the APO 202 trial receiving placebo. No SAEs were reported in the APO 301 and APO 302 trials. Three patients in the APO 202 trial and one patient in the APO 302 trial receiving apomorphine experienced chest pain that did not result in hospitalization. These were not considered SAEs by the authors.

Withdrawals Due to Adverse Events

Only two reported incidents of AEs resulting in withdrawal from treatment were found in the APO 202 trial. One patient receiving apomorphine dropped out due to chest pain and the

other cited nausea and vomiting as reasons for treatment discontinuation. There were no withdrawals in the APO 301 and APO 302 trials due to AEs.

Mortality

No deaths were reported in any of the three trials.

Notable Harms

Dyskinesia, injection site reaction, postural hypotension, and impulsive/asocial behaviour were considered as the notable harms or harms of special interest for this review. However, no study had data on impulsive/asocial behaviour.

Dyskinesia was reported more frequently as an AE by patients receiving apomorphine than those receiving placebo (35% versus 11%) in the APO 202 trial. In the APO 301 trial, dyskinesia was not reported as an AE and was found as a frequent characteristic of apomorphine injection. Only two patients in the APO 302 trial reported an AE for dyskinesia. The dyskinesia scores across all trials were found to be mild to moderate on average.

Injection site reactions (including bruising, pain, skin reaction, and nodule development) were seen in 14 patients in the APO 202 trial, and in only 2 and 1 patients in the APO 301 and APO 302 trials, respectively.

All three studies excluded any patients with a history of significant orthostatic hypotension, and this was not reported as an AE outcome in APO 202 and APO 301. However, upon request for additional information for blood pressure by Health Canada, the sponsor of the APO 301 trial provided data for clinically defined orthostatic hypotension (decreases in SBP > 20 mm Hg or decreases in DBP > 10 mm Hg). The results showed that the proportion of patients with clinically significant orthostatic hypotension was higher with apomorphine than with placebo at 20 minutes post-dose (SBP decrease of 6% versus 0%; DBP decrease of 31% versus 12%). In the APO 302 trial, orthostatic hypotension was defined as a ≥ 20 mm Hg drop in SBP or ≥ 10 mm Hg drop in DBP (criterion 1) or a drop in SBP of ≥ 30 mm Hg to a standing SBP of ≤ 90 mm Hg, or a drop in DBP of ≥ 20 mm Hg to a standing DBP of ≤ 50 mm Hg (criterion 2). A total of 25 patients had blood pressure measurements that fulfilled criterion 1 for orthostatic hypotension, 12 in the pooled apomorphine groups and 13 in the pooled placebo group. One placebo patient met criterion 2; however, it did not occur following treatment administration but instead on a prior APO 401 baseline visit. Of the 12 orthostatic patients receiving apomorphine or apomorphine + 2, four experienced orthostasis at baseline or pre-dose assessment, five experienced orthostasis at both pre-dose and post-dose assessments, and three patients experienced orthostasis exclusively after administration of apomorphine. Symptoms of orthostatic hypotension were found only in two apomorphine-treated patients, one of which was not reported as related to apomorphine dosing. Overall, the changes in SBP and DBP from a sitting to a standing position were not different between the treatment groups, both pooled and pairwise, at 20 and 90 minutes post-dose (data not shown).

Discussion

Summary of Available Evidence

The evidence for this CDR submission was obtained from two published and one unpublished double-blind, placebo-controlled, multi-centre trials, all of which were considered pivotal by Health Canada. One study, APO 202, was a phase II trial conducted in both in-patient and outpatient settings for a total duration of one month. APO 301 and APO 302 were phase III trials, conducted within one to two days. APO 202 provided evidence for therapeutic response to apomorphine, while APO 301 and APO 302 provided evidence for continued therapeutic efficacy with apomorphine treatment. Notably, APO 301 had a crossover design, whereas the other two were parallel-group trials. Patients in APO 202 (N = 29) were apomorphine naive, whereas patients in APO 301 (N = 17) and APO 302 (N = 62) were exposed to apomorphine for a minimum of three months. Patients across all three trials were on optimized levodopa and other anti-PD medications.

All trials used adequate methods to conceal treatment assignment by supplying apomorphine and placebo in identical ampoules, and the randomization scheme was clear in APO 202 but not in the others. The similarity of background characteristics as well as high study completion rates between the treatment groups in all trials suggest that the randomizations were preserved throughout the studies. However, due to the nature of the indication and the differences between the pre-dose “off” and post-dose “on” states that were likely more apparent in the apomorphine-treated group than in the placebo group, blinding of treatment allocation may not have been fully maintained. This may overestimate the treatment effect, particularly if the ability of patients or study personal to deduce treatment allocation occurs differentially between the treatment groups for the outcomes prone to subjective assessment by the patients or study personnel. No sensitivity analyses were done to address any potential error in effect size estimation resulting from such potential bias.

The ranges of dose received by the patients in the three trials varied and were not always consistent with the dose approved by Health Canada. However, the mean daily dose in APO 202 (outpatient phase), APO 301, and APO 302 were 5.8 mg/dose, 3.9 mg/bolus, and 3.8 mg/dose (which varied on treatment day), respectively; these were all within the manufacturer-recommended maximum dose of 6 mg for individual doses. Notably, some patients likely received more than 6 mg per dose since the mean doses were close to the Health Canada–recommended and manufacturer-recommended maximum limit for individual injections, which would not be commonly seen according to the clinical expert. The majority of the patients received three or fewer injections per day.

The primary efficacy outcome in all three trials was based on changes in the post-dose UPDRS-III motor score. In the APO 202 trial, an improvement of ≥ 30% in the UPDRS motor score following the dopaminergic challenge was set as one of the inclusion criteria for randomization, and a UPDRS motor score of ≥ 90% of the response seen following the dopaminergic challenge test was used to determine TED for apomorphine. In two recently published studies,[4] median improvements of approximately 11% and 37% in UPDRS motor score were seen following levodopa challenge and treatment with deep brain stimulation, respectively, among late-stage PD patients. This indicates that the ≥ 30% and ≥ 90% cut-off values chosen for dopaminergic response and treatment efficacy, respectively, were not inappropriately low. This outcome, in addition to dyskinesia assessment, is commonly

assessed in most studies involving motor function improvement in PD patients. However, a number of less well-known tests such as HTT and WSST were performed as additional end points. No evidence on quality-of-life–related parameters was available, a significant issue for PD patients. Patient-reported data on the onset, incidence, frequency and duration of "off" and "on" episodes were collected using daily diaries or self-declaration, which may be particularly susceptible to biased reporting if unblinding occurred. However, due to the lack of any method to control for type I error resulting from multiple testing as well as the possibility of underpowered analyses, results from these outcomes should be interpreted with this in mind and considered exploratory. In the APO 302 trial, the primary contrast was between pooled apomorphine and pooled placebo since there were no statistically significant differences between the placebo and placebo + 2 group using parametric and non-parametric analyses. The safety profile of apomorphine treatment was more comprehensively assessed in APO 202 due to its relatively longer duration, and the known side effects of apomorphine (dyskinesia, nausea, and somnolence) were found in greater proportion among apomorphine-treated patients. Due to the short follow-up period, it may not have been possible to capture the full AE profile of apomorphine treatment. However, the supporting studies, APO 303 and its parent study APO 401, provided longer-term safety data of continued apomorphine treatment.

Interpretation of Results

Efficacy

The primary objective of the APO 202 trial was to measure the therapeutic efficacy of the highest tolerable dose of apomorphine during "off" episodes induced by withholding regular anti-PD medications. There are several types of "off" episodes, including spontaneous "off" or "end-of-dose wearing off." Demonstrating efficacy in induced "off" episodes represented the worst-case scenario, and would likely be effective during "end-of-dose wearing off" episodes or spontaneous "off" episodes according to the clinical expert. Treatment efficacy during more likely spontaneous "off" episodes was evaluated in the outpatient phase as a secondary objective. APO 301 and 302, in contrast, measured the continued efficacy of apomorphine among treatment-experienced patients in their usual doses following the spontaneous "off" or "end-of-dose wearing off" episodes after their first morning dose of anti-PD medications.

The primary end point in all three trials was change in UPDRS-III motor score at or around 20 minutes post-dose. There was a mean reduction in post-dose UPDRS-III score of greater than 61%, 47%, and 58% from pre-dose score in APO 202, APO 301, and APO 302, respectively, which was statistically significantly different compared with placebo in all cases. The mean difference in UPDRS-III score seen in the APO 202 trial following apomorphine administration at patients' TED was similar in magnitude as that seen with levodopa treatment. The mean post-dose reductions in UPDRS-III score of 23.8, 21.3, and 24.2 in APO 202, APO 301, and APO 302, respectively, were all considered clinically significant observable changes according to the clinical expert as well as the MCID for UPDRS-III.

A number of additional outcomes were measured as secondary end points, such as UPDRS-III score at different time points, DRS score, HTT score, WSST score, and duration of "off" episodes. However, analyses of these secondary variables were not adjusted for multiple statistical comparisons; therefore a statistical difference may not be conclusive and should be interpreted with this in consideration. In APO 301, patients receiving apomorphine

had more than 35% and 30% reduction in mean UPDRS-III score 10 minutes and 60 minutes post-dose, respectively. In APO 302, there was also a reduction in mean UPDRS-III score of more than 48% and 13% after 10 minutes and 90 minutes post-dose, respectively, in the pooled apomorphine group. The severity of dyskinesia was measured using DRS in all three trials. In APO 202, an increase in median dyskinesia score was seen following apomorphine treatment at a level similar to that of levodopa treatment, and the score was numerically higher than in the placebo group. The median DRS score was also reported to be numerically higher among the apomorphine-treated patients in the APO 301 and APO 302 trial at 10 and 20 minutes. The HTT was done only during the in-patient phase of APO 202, and a mean change of 88% from pre-dose "off" state was seen in the apomorphine-treated group, which was numerically higher than the −4% change seen in the placebo group and higher than the 55% change elicited by levodopa. Change in WSST score was measured at one time point in APO 202 and multiple time points in APO 302. During the in-patient phase of APO 202, a 65% reduction in median WSST score was reported in the patients treated with the TED of apomorphine, while a gradual decrease in median WSST score over the course of 40 minutes was seen in APO 302 patients. The average duration of "off" episodes was assessed during the outpatient phase in APO 202 only, and a numerically greater reduction in mean daily "off" time of approximately 2 hours from baseline was registered in the apomorphine group without any concomitant change in the placebo group.

Other notable outcomes in this review include time to onset of relief from symptoms and proportion of injections resulting in aborting "off" events. These variables were also not adjusted for multiplicity; therefore interpretation of these results should not be considered conclusive. Time to response was measured in the in-patient phase of APO 202 using clinically determined change in UPDRS-III motor score. While UPDRS-III was administered in both treatment groups at around the same time (within 20 minutes post-dose), the mean time to response in the apomorphine-treated group was numerically almost half of the response time seen in the placebo group (22.1 versus 44.8 minutes). In contrast, the times to response in the APO 301 and APO 302 trials were measured following patients self-declaring their perceived "on" state; those unable to declare an onset of symptom relief within the time frame of the study had values imputed as 60 and 40 minutes, respectively. Apomorphine-treated patients in the APO 301 trial had a median time to response of 15 minutes, which was sooner than in the placebo group (60 minutes). After excluding patients who did not explicitly declare an onset of relief, the difference was no longer meaningful. In the APO 302 trial, both apomorphine-treated and placebo-treated patients had a similar median time to response, although relief occurred numerically sooner in the apomorphine group (5 minutes versus 7.5 minutes). Frequency of "off" episodes and proportion of injections that successfully reversed "off" events were measured only in the outpatient phase of APO 202 using patients' diaries. The change in the daily number of "off" events was minimal in both the treatment groups; however, more than 95% of "off" events were aborted with apomorphine injection as opposed to 23% with placebo injection.

Harms

Overall, the three pivotal trials had a short follow-up duration; therefore it may not be possible to see the spectrum of all AEs during these trials. However, the trials discussed in Appendix 6 (APO 303 and APO 401) provided longer-term safety data associated with apomorphine treatment. The number of patients with AEs was higher in the APO 202 trial compared with the APO 301 and APO 302 studies, and the vast majority of the patients in the long-term APO 303 and APO 401 trials reported at least one AE. Most of the AEs found

in patients were known side effects of apomorphine or dopaminergic treatment such as yawning, somnolence, nausea, dizziness, dyskinesia, injection site reactions, and hallucinations, and were considered mild to moderate in severity.

Injection site reactions were the most common AE reported in APO 202, and these AEs were considered mild without any associated pain. Previous reports have shown mild to moderate hematomas and subcutaneous nodule formation with subcutaneous pen injections of apomorphine.[29] There were no AEs reported in the apomorphine group on treatment days in the APO 301 trial while two unrelated AEs were found on non-treatment days. This was unexpected, since APO 302 and other single-dose and multiple-dose pharmacokinetic studies among treatment-experienced patients found common AEs typically associated with apomorphine treatment.[4] The Health Canada Review Report indicated that this might be due to the differential nature of AE reporting/recording in European studies (where APO 301 was conducted), after a similar trend in discrepancy in AE reporting was found for several central nervous system drugs.[4] Dyskinesia was not reported as an AE in this trial, but approximately 70% of apomorphine-treated patients experienced dyskinesia that ranged from mild to moderate in severity and was transient. In contrast, eight and two cases of dyskinesia were reported as AEs in the APO 202 and APO 302 trials, respectively; however, the severity of dyskinesia on average was mild to moderate and increased in the apomorphine group.

Patients in the APO 301 trial experienced a decrease in sitting SBP and DBP following apomorphine dosing. However, orthostatic hypotension was not reported by the manufacturer before formal request from Health Canada (Clarifax September 16, 2016).[4] It was then reported that a numerically higher proportion of patients receiving apomorphine experienced clinically defined orthostatic hypotension at 20 minutes post-dose, but less so at 60 minutes. Similar decreasing patterns in SBP and DBP were also found with apomorphine treatment at 20 minutes post-dose in the APO 302 trial; pressures returned to pre-dose values by 90 minutes. While orthostatic change in blood pressure was registered in both treatment groups post-dose, it was noted that only three patients had orthostasis exclusively after dosing, indicating that the majority of the orthostasis cases were not exclusively treatment-related. In addition, the proportion of patients reporting orthostasis was not more than 15% in the apomorphine-treated group. Since patients in both APO 301 and APO 302 had received apomorphine treatment for an average of 2.5 years and 1.2 years, respectively, it was suggested that the drop in treatment-emergent blood pressure is not limited to the initial dosing period and may persist for the entire duration of the treatment.

No serious or significant AEs were registered in the APO 301 and 302 trials, whereas four such cases were reported in APO 202 and involved chest pain, pressure, or angina symptoms. One patient in the apomorphine group discontinued the study due to chest pain, but it was not considered serious and the patient had concurrent cardiovascular conditions. Another apomorphine-treated patient cited nausea and vomiting as a reason for treatment discontinuation before the outpatient phase of the study. One patient receiving placebo in the APO 301 trial and two patients receiving placebo in the APO 302 trial discontinued due to lack of treatment effectiveness.

The APO 401 trial and its substudy, APO 303, discussed in Appendix 6, were designed to assess long-term safety associated with apomorphine treatment. Overall, patients in these trials administered apomorphine intermittently for over a year or longer for treatment of motor fluctuations. The vast majority (> 90%) of the patients in both trials reported at least one AE, and the AEs were mild to moderate in severity. Most common AEs were predictable side effects of apomorphine treatment as described above and included nausea, vomiting,

dyskinesia, dizziness, somnolence, and injection site reactions. In the APO 303 trial, which consisted of an in-patient dose-titration phase and an outpatient treatment phase, there was a dose-dependent and time-dependent increase of AEs particularly during the in-patient crossover period. SAEs occurred in four patients (7.1%) in the APO 303 trial, of which one episode of syncope and sinus arrest was considered treatment-related. On the other hand, a total of 199 (36%) SAEs were registered in the APO 401 trial, of which 187 led to study discontinuations resulting from AEs. The majority of the remaining patients extended their treatment beyond one year. Twenty-seven of the recorded SAEs may have been related to apomorphine treatment, of which syncope, drug-induced psychosis, postural hypotension, and fall were the most frequent events. An increase in symptomatic orthostatic hypotension was associated with apomorphine injection.

Potential Place in Therapy[2]

Since its introduction into clinical practice almost 50 years ago, levodopa remains the most effective treatment for the motor manifestations of PD. However, levodopa is only a symptomatic treatment. It does not slow the underlying neurodegenerative process in PD, and the number of functioning nigrostriatal pathway neurons continues to decline. As the number of remaining functioning nigrostriatal neurons falls, the midbrain's ability to convert levodopa to dopamine and thereby stimulate the striatum becomes increasingly impaired. Clinically, this decline in the nigrostriatal population is experienced by patients as a gradual transition from the initial months or years in which levodopa produces a sustained, continuous improvement in motor function to a state in which individual doses of levodopa produce increasingly shorter periods of improvement, which wear off quickly. As PD advances, more and more the patient alternates between "on" periods, when they are mobile, and "off" periods, when they are immobile. Generally the fluctuation between the "on" and "off" states can be related to when individual doses of levodopa are administered. To some extent, this fluctuation can be minimized by spacing levodopa doses closer together and using additional drugs such as sustained-release levodopa preparations, drugs that inhibit the metabolism of levodopa, or direct dopamine agonists (the latter generally have a longer duration of action than levodopa but are also unfortunately generally less effective). Although patients can learn to adapt to these fluctuations to some extent, the fluctuations can be unpredictable, severe, and have a major impact on their ability to carry out tasks of daily living.

Apomorphine has long been known to be an effective and rapidly acting dopamine agonist. Its use has been limited because of its poor oral bioavailability. However, when administered by injection in response to an "off" state, apomorphine is able to act rapidly and offers patients the possibility of a quick (within a half-hour) improvement in mobility, although the benefit rarely lasts more than an hour. Injectable apomorphine is thus likely to find a useful niche as an additional therapy for PD patients who experience prominent fluctuations between "on" and "off" states during the day (whether clearly related to the timing of levodopa doses or occurring unpredictably), as well as for those who are disabled by impaired mobility upon awakening in the morning (i.e., before they have taken their first morning dose of levodopa).

The patients most likely to find injectable apomorphine helpful are those with moderately advanced PD (disabled, but still ambulatory and at least semi-independent). Identification of such patients would be part of routine neurological follow-up and would not require any new or specific diagnostic testing.

[2] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

Conclusions

In this CDR systematic review, three randomized, double-blind, placebo-controlled trials were included to assess the therapeutic efficacy and safety of intermittent, subcutaneous apomorphine as an adjunct therapy to standard anti-PD medications to treat “off” episodes (e.g., “end-of-dose wearing off” or unpredictable “off”) in late-stage PD patients (H&Y stage 2 to 4).

Overall, a statistically significant improvement in motor function based on the primary efficacy parameter — UPDRS-III motor score from baseline to 20 minutes post-dose — was found with apomorphine treatment compared with placebo in all studies. Changes in motor function were measured using a number of additional secondary outcome variables (e.g., HTT, WSST, DRS), and all showed numerical improvements compared with baseline or pre-dose “on” values. However, due to the lack of control for multiplicity in any of the trials, results from these outcomes could not be interpreted with reference to statistical or clinical significance. Patients treated with apomorphine reported a decrease in total daily “off” hours, successfully aborting most “off” episodes, and the time to onset of symptom relief was sooner than that in the placebo group; however, these outcomes were also not controlled for multiple statistical testing. In terms of AEs, the short-term studies confirmed the side effects that are commonly associated with apomorphine treatment, including but not limited to dyskinesia, orthostatic hypotension, falls, somnolence, dizziness, yawning, hallucination, and nausea/vomiting. SAEs were not frequently reported with apomorphine treatment, and the AEs were mostly mild to moderate in severity. The long-term studies found similar AEs as reported in the short-term studies, but long-term efficacy could not be assessed.

Appendix 1: Patient Input Summary

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Groups Supplying Input

Two patient groups, Parkinson Canada (PC) and Parkinson Society British Columbia (PSBC), provided input for this submission.

PC is a national registered charity organization, operating since 1965, that provides support services and education for patients with Parkinson's disease (PD), their families and caregivers. In addition, PC advocates for patients' issues and supports research in this area through The Parkinson Canada Research Program. As a national registered charity, PC receives funding from donors. For this submission, PC received input from jurisdictions outside of Canada; however there was no exchange of funds for this activity. Additionally, no financial ties were disclosed with organizations or companies that can be benefiting from this drug.

PSBC is a non-profit organization, operating since 1969, and is dedicated to offering support, information, and fundraising for programs and research aiming to improve the lives of patients with PD. Its operation is funded and supported by donations from individuals, members, corporations, foundations, and volunteers. In preparation of the submission, information from a helpline and blogs of Parkinson UK and the National Parkinson Foundation in the US were used. Further, PSBC consulted Dr. Andrew Lees, a professor of Neurology at the National Hospital for Neurology and Neurosurgery, Queen Square, London, and University College London, due to his vast experience with clinical treatment and research in PD. Dr. Lees is a strong proponent of apomorphine and introduced its use in Britain for advanced stages of PD. The following quotes summarize his views in apomorphine: "I think it is almost criminal that such an efficacious drug has taken so long to reach Canada" and "… no dispute that it is a treatment far more effective than oral or patch dopamine agonists and a treatment which may have a much lower incidence of impulse control disorders and dopamine dysregulation when used as pump therapy."

2. Condition-Related Information

PC conducted an online survey during June 28 to July 17, 2017, both nationally and internationally. A total of 863 responses were registered, of which fewer than 3% were from the US and Europe and just over half were from Ontario; however, there were respondents representing every province. Sixty-one per cent of the respondents were people suffering from PD, while caregivers accounted for the rest. Information from five patients experienced with apomorphine was also collected.

The PSBC submitted report-sourced information from Parkinson UK and the National Parkinson Foundation 1-800 helpline, referral service, and online blogs. In addition, documents provided by Dr. Lees were used in the PSBC submission. Although exact statistics were not provided, it was indicated that very few callers with experience using apomorphine were documented.

PD is a progressive neurodegenerative disease characterized by an inability to move normally. Patients frequently present motor problems such as resting tremor, rigidity, slowness of movement, and postural instability. Other notable symptoms include hypomimia, hypophonia, micrographia, alterations in mood and memory, sleeping difficulty and

unexpected sleep, constipation, pain, and fatigue. The symptoms generally worsen over time without proper treatment.

In the PC survey, respondents ranked their symptoms as most important to control in the following way: slowness and stiffness, balance impairment, cognitive changes and memory, and muscle rigidity. An overwhelming majority of the PC survey respondents described experiencing a loss of confidence in activities of daily life. Nearly 40% of respondents indicated that Parkinson's has negatively impacted their ability to engage in recreational activities and maintain social or family life.

The loss of confidence was in part due to the "wearing off" effect of treatments, resulting in "off" times when a resurgence of motor and non-motor Parkinson's symptoms (e.g., freezing episodes, tremor, mood swings, panic attacks, etc.) occurs. "Off" times are unpredictable for many patients and negatively impact quality of life, as significant planning and coordination are required to carry out daily activities. Other aspects of quality of life negatively impacted by PD symptoms include socializing and relationships, recreational activities, household chores, driving, reading and writing, etc. Inability to work was also a significant concern, as it adds financial and emotional stress for patients and their family.

"Parkinson's disease, even on the best of days, severely limits one's daily activity. Off-periods bring everything to a halt and are disorienting and uncomfortable. Adding extra functionality to a day makes a significant difference when one has only a few hours to begin with."

Caregivers responding to the PC survey expressed concern associated with increased dependence and the unpredictability of "off" times with the progression of disease. Increased demands from patients with PD created a lack of time for the caregivers, which then translated to difficulty in maintaining social, recreational, and household activities on their part.

3. Current Therapy–Related Information

Currently available therapies to minimize PD symptoms include medications (e.g., levodopa, carbidopa), surgical procedures (e.g., deep brain stimulation), psychotherapy, and other forms of therapy (e.g., physiotherapy, occupational therapy, speech therapy, exercise).

Levodopa, which is converted into dopamine in the brain, is considered the gold standard treatment in PD. Although it reduces bradykinesia and rigidity and improves movement, its effects wear off quickly due to its chemical nature, and levodopa is associated with gastrointestinal side effects. As a protein, levodopa competes for absorption with other proteins; therefore meals need to be timed and adjusted if rich in protein. Patients on levodopa unfortunately experience bradykinesia or involuntary writhing during the effective or "on" period as a side effect of the drug, while "off" periods lead to even more disabling conditions such as problems in breathing and swallowing in addition to rigidity, dystonia, tremor, and freezing.

DUODOPA is a mixture of levodopa and carbidopa that is continuously pumped directly into the small intestine throughout the day among patients with advanced PD symptoms nonresponsive to other medications. However, high cost, difficulty in access, recovery time, and dose titration limit the administration of this therapy.

Deep brain stimulation is a surgical procedure involving the surgical implantation of a neurostimulator, which blocks abnormal nerve signals that would otherwise cause

debilitating symptoms of PD, such as tremor, rigidity, stiffness, slowed movement, and walking problems. Patients who underwent deep brain stimulation regained their ability to work and reduced the requirement for or dose of other medications significantly or entirely. However, deep brain stimulation is associated with a significantly long wait time (e.g., five years in British Columbia), in addition to the requirement for multiple travels, a recovery period, and optimization in the patients.

Commonly cited difficulties in receiving treatments include swallowing; compliance with dose, time and frequency of medications; and interaction between drugs and meals. Medications for PD need to be adjusted for dosage and balanced between benefits and harms. Treatment “on” and “off” periods need to be considered to plan daily activities and functionalities as patients become more reliant on their medications over time. Problems associated with current therapies can be categorized into clinical side effects (disturbed sleep, nausea, constipation, dyskinesia, fatigue, and hallucinations) and access to treatment (wait time, travel, insurance requirements, and cost). In 2012-2013, an estimated $1.12 billion was spent on PD-related costs in just British Columbia alone, and this is projected to double by 2031.

4. Expectations About the Drug Being Reviewed

Seventy per cent of the PC survey respondents indicated that new medications that are longer lasting and that limit or eliminate “off” times, which is a significant concern in many PD treatments, are needed. A reduction in “off” periods would inevitably improve patients’ ability to function and quality of life by allowing any social or daily activities that require leaving their home. Management of debilitating PD symptoms (e.g., freezing; inability to walk; difficulty in breathing, swallowing and speech; hallucination; and maintaining posture and normal movement, which might otherwise cause fall-associated injuries) and side effects was also high on the list of patients’ expectation from PD medications.

“Medication that takes more rapid effect, does not lose its effectiveness before the next dose is due (effectiveness wears off), and is more effective in treating inertia (freezing) and inability to walk; also medication to permit intelligible and normal speech. These improvements would enable more normal mobility and communication with family and others.”

Apomorphine is used as an injection, which makes it easy to administer; however, patients reported difficulty using it compared with other medications because fresh needles and comfort in self-injecting are crucial for this mode of therapy. If the symptoms have already started, injection may not be possible without the help of others, which can be challenging outside of home or in a public place.

Most patients reported an improvement in treatment “wearing off” effects using apomorphine, reducing “off” times and thereby improving quality of life. Effectiveness in management of PD symptoms has varied: no benefits and subsequent discontinuation of apomorphine injection was reported by one patient; another reported the use of a pump form of the drug instead of an injectable pen after clear benefits were observed and maximum allowable daily amount of apomorphine was reached. Even for patients receiving more advanced and efficacious deep brain stimulation treatment, carrying injection pens is not uncommon in case of sudden PD symptoms such as dystonia.

5. Additional Information

Given the nature of PD symptoms, almost all aspects of patients' lives are affected by it. Access to medications that minimize symptoms and side effects in addition to "off" periods are crucial to patients' daily functioning and quality of life. The request for coverage for apomorphine was shared by clinicians and patients to ensure its affordability and accessibility, which would otherwise pose a significant economic burden on the patients and their families as well as the health care system overall.

"Life is good, but when I'm stuck, locked in my own body, helpless and sad. When I can´t communicate with the outside world — if that's the way it will be, I do not really want to live. But even from the darkest moments, the rebirth is "hallelujah moment" when the rigidity disappears and life returns and it's good to live again."

Appendix 2: Literature Search Strategy

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates via Ovid, Embase (1974–) via Ovid, and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Movapo (apomorphine) and Parkinson's disease.

Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and controlled clinical trials. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results.

The initial search was completed on August 3, 2017. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee on December 13, 2017. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters* checklist (https://www.cadth.ca/grey-matters):

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (Free)
- Internet Search.

Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	August 3, 2017
Alerts:	Weekly search updates until December 13, 2017
Limits:	No date or language limits were used Human filter was applied Conference abstracts were excluded Filters were applied to limit the retrieval to: health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and controlled clinical trials

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
?	Truncation symbol for one or no characters only
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.rn	CAS registry number
.nm	Name of substance word
ppez	Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

CADTH

MULTI-DATABASE STRATEGY	
/	At the end of a phrase, searches the phrase as a subject heading
1	exp Apomorphine/
2	(Apokyn or Apomorphin* or Spontane or ApoGO or Apo GO or Uprima or Ixense or Movapo or Britaject or Apokinon or Apomorfin or Tocris 2073 or Tocris2073).ti,ab,kf,ot,hw,nm.
3	("EINECS 206 243 0" or EINECS 2062430 or EINECS2062430 or NSC 11442 or NSC11442 or pomorphini hydrochloridium or UNII 9K13MD7A0D or "58004" or 5800 4 or "58 00 4" or HSDB 3289 or N21FAR7B4S).ti,ab,kf,ot,hw,nm,rn.
4	(314 19 2 or "314192" or 31419 2 or "58004" or 5800 4 or "58 00 4").rn,nm.
5	1 or 2 or 3 or 4
6	exp Parkinson Disease/
7	(Parkinson* or PD).ti,ab,kf,ot,hw.
8	6 or 7
9	5 and 8
10	9 use ppez
11	exp *apomorphine/
12	(Apokyn or Apomorphin* or Spontane or ApoGO or Apo GO or Uprima or Ixense or Movapo or Britaject or Apokinon or Apomorfin or Tocris 2073 or Tocris2073).ti,ab.
13	("EINECS 206 243 0" or EINECS 2062430 or EINECS2062430 or NSC 11442 or NSC11442 or pomorphini hydrochloridium or UNII 9K13MD7A0D or "58004" or 5800 4 or "58 00 4" or HSDB 3289 or N21FAR7B4S).ti,ab.
14	11 or 12 or 13
15	exp *Parkinson disease/
16	(Parkinson* or PD).ti,ab.
17	15 or 16
18	14 and 17
19	18 use oemezd
20	10 or 19
21	exp animals/
22	exp animal experimentation/ or exp animal experiment/
23	exp models animal/
24	(rat or rats or mice or mouse or animal model).ti.
25	nonhuman/
26	exp vertebrate/ or exp vertebrates/
27	21 or 22 or 23 or 24 or 25 or 26
28	exp humans/
29	exp human experimentation/ or exp human experiment/
30	28 or 29
31	27 not 30
32	20 not 31
33	meta-analysis.pt.

MULTI-DATABASE STRATEGY	
34	meta-analysis/ or systematic review/ or meta-analysis as topic/ or “meta analysis (topic)”/ or “systematic review (topic)”/ or exp technology assessment, biomedical/
35	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf,kw.
36	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kf,kw.
37	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kf,kw.
38	(data synthes* or data extraction* or data abstraction*).ti,ab,kf,kw.
39	(handsearch* or hand search*).ti,ab,kf,kw.
40	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kf,kw.
41	(met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kf,kw.
42	(meta regression* or metaregression*).ti,ab,kf,kw.
43	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
44	(medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.
45	(cochrane or (health adj2 technology assessment) or evidence report).jw.
46	(comparative adj3 (efficacy or effectiveness)).ti,ab,kf,kw.
47	(outcomes research or relative effectiveness).ti,ab,kf,kw.
48	((indirect or indirect treatment or mixed-treatment) adj comparison*).ti,ab,kf,kw.
49	(meta-analysis or systematic review).md.
50	or/33-49
51	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial).pt.
52	Randomized Controlled Trial/
53	exp Randomized Controlled Trials as Topic/
54	“Randomized Controlled Trial (topic)”/
55	Controlled Clinical Trial/
56	exp Controlled Clinical Trials as Topic/
57	“Controlled Clinical Trial (topic)”/
58	Randomization/
59	Random Allocation/
60	Double-Blind Method/
61	Double Blind Procedure/
62	Double-Blind Studies/
63	Single-Blind Method/
64	Single Blind Procedure/
65	Single-Blind Studies/
66	Placebos/
67	Placebo/
68	Control Groups/
69	Control Group/
70	(random* or sham or placebo*).ti,ab,hw,kf,kw.

MULTI-DATABASE STRATEGY	
71	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.
72	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.
73	(control* adj3 (study or studies or trial*)).ti,ab,kf,kw.
74	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw.
75	allocated.ti,ab,hw.
76	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw.
77	or/51-76
78	32 and 50
79	32 and 77
80	78 or 79
81	80 not conference abstract.pt.
82	remove duplicates from 81

OTHER DATABASES		
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.	
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.	

Grey Literature

Dates for Search:	July 2017
Keywords:	Movapo and Parkinson's Disease and relevant synonyms
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: a practical tool for searching health-related grey literature* (https://www.cadth.ca/grey-matters) were searched:

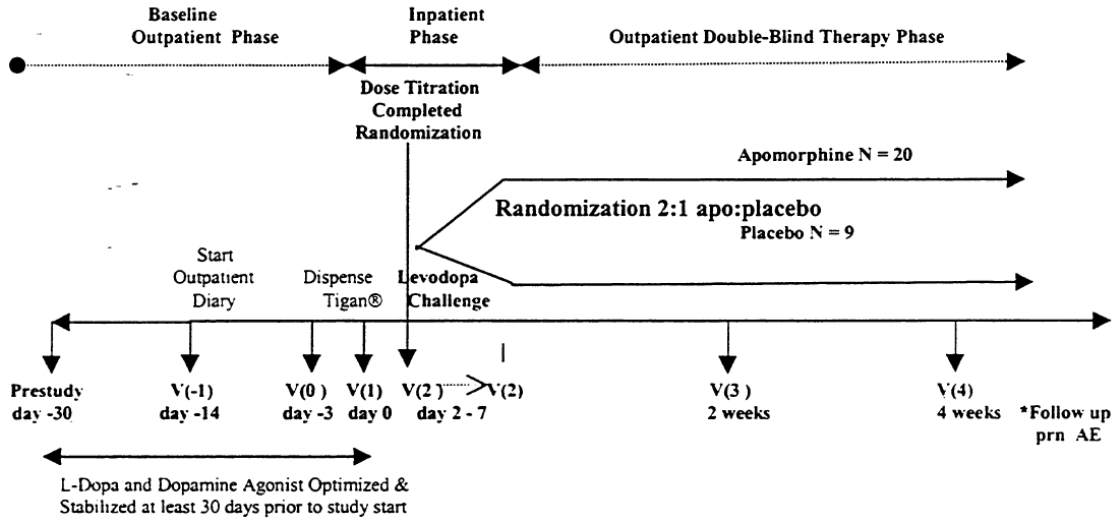
- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (Free)
- Internet Search.

Appendix 3: Excluded Studies

Reference	Reason for Exclusion
PAHWA et al.[30]	Intervention not of the interest (not recommended titration schedule)
LEWITT et al.[10]	Intervention not of the interest (not recommended titration schedule)
TROSCH et al.[31]	Intervention not of the interest (not recommended titration schedule)
OSTERGAARD et al.[29]	Intervention not of the interest (not recommended titration schedule)
Hughes et al.[32]	Uncontrolled study
PIETZ et al.[33]	Uncontrolled study
Frankel et al.[34]	Uncontrolled study
VAN et al.[35]	Intervention not of the interest (not recommended titration schedule)
NOMOTO et al.[36]	Phase II trial
HATTORI et al.[37]	Intervention not of the interest (not recommended starting dose)
Isaacson et al. 2017[38]	Population not of interest (not the PD with “off” period)
Kompoliti et al. 2000[39]	Population not of interest (not the PD with “off” period)

Appendix 4: Detailed Outcome Data

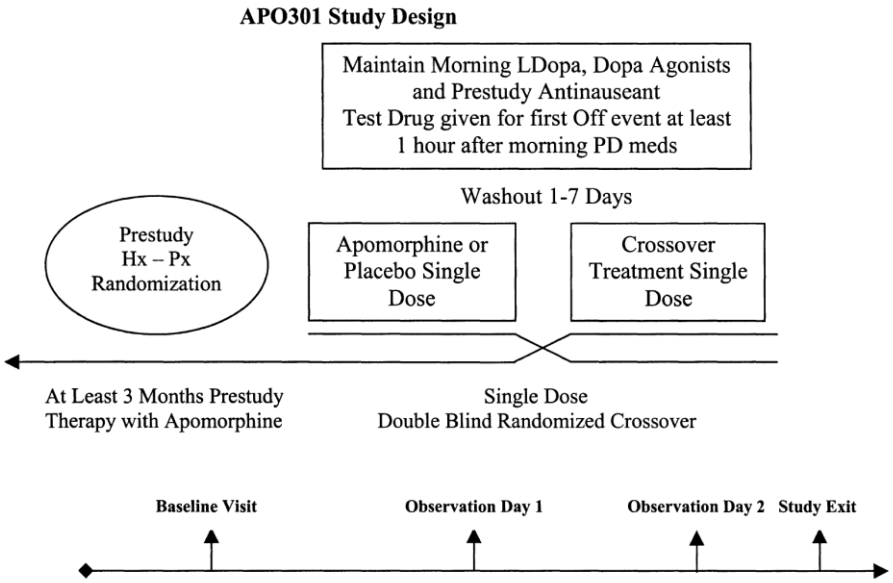
Figure 2: Diagram of APO 202 Study Design



AE = adverse event; L-Dopa = levodopa; V = visit;

Source: APO 202 Clinical Study Report.[1]

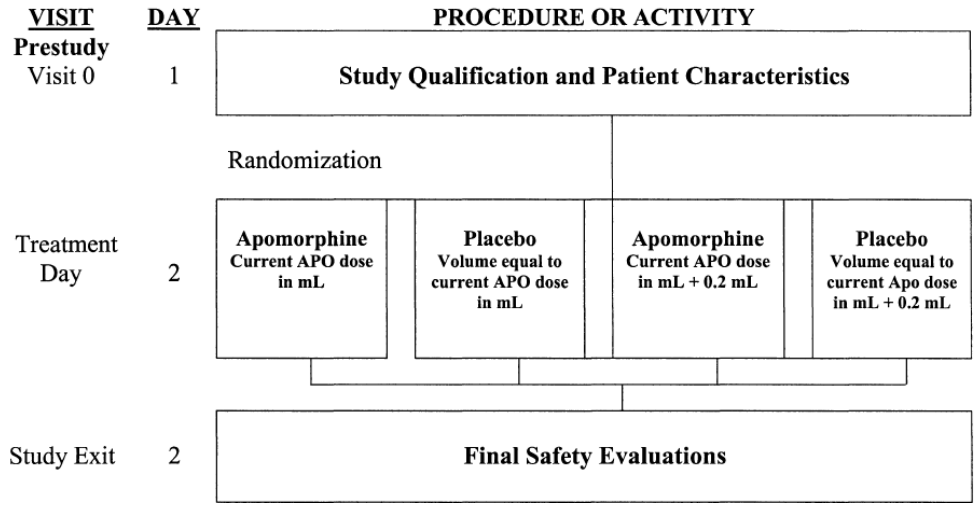
Figure 3: Diagram of APO 301 Study Design



LDopa = levodopa; HX = History (medical), PD = Parkinson's disease; PX = Physical Examination.

Source: APO 301 Clinical Study Report.[2]

Figure 4: Diagram of APO 302 Study Design



APO = apomorphine.

Source: APO 302 Clinical Study Report.[3]

Table 22: Response Ratio of Outcome Parameters in APO 202

Outcome Parameter, Response Ratio[a]	APO (N = 20[b] or N = 19[c])	PLB (N = 9)	*P* Value[d]
UPDRS Motor Exam Score			
Mean (SE)	0.96 (0.06)	0.00 (0.08)	< 0.0001
Median	0.97	0.00	< 0.0001
Hand-Tapping Test Score			
Mean (SE)	1.58 (0.59)	−0.15 (0.11)	0.05
Median	0.84	−0.04	0.0001
WSST Score			
Mean (SE)	1.00 (0.09)	−0.04 (0.12)	< 0.0001
Median	1.00	0.00	< 0.0001

ANOVA = analysis of variance; APO = apomorphine; HTT = hand-tapping test; PLB = placebo; SE = standard error; UPDRS = Unified Parkinson's Disease Rating Scale; WSST = Webster step-seconds test.

[a] Response ratio = Per cent change in raw score following injection of test medication / Per cent change in raw score following injection of levodopa.

[b] N = 20 for UPDRS motor score exam.

[c] N = 19 for HTT and WSST scores because 1 patient dropped out due to nausea/vomiting following UPDRS assessment at 0.6 mL dosing; therefore, HTT and WSST scores could not be assessed.

[d] *P* values for mean ratio and median ratio were calculated using ANOVA and Wilcoxon rank sum test, respectively.

Source: APO 202 Clinical Study Report.[1]

Table 23: Sequence Effect in UPDRS-III Score Change from Pre-Dose in APO 301

Outcome Parameter	APO (N = 17)	PLB (N = 17)	*P* Value[b]	*P* Value[c]
Time-Course, Mean (SE)				
Pre-dose score	41.3 (2.5)	40.1 (2.2)		
10 minutes post-dose	25.9 (3.4)	37.4 (2.9)		
Change from pre-dose	−15.4 (3.7)	−2.7 (2.0)	0.24	0.27
% change from pre-dose	−35.9 (7.4)	−6.7 (5.0)	0.12	0.34
20 minutes post-dose[a]	21.3 (3.5)	37.1 (2.3)		
Change from pre-dose	−20.0 (3.6)	−3.0 (2.2)	0.27	0.07
% change from pre-dose	−47.4 (8.6)	−5.9 (5.0)	0.15	0.15
60 minutes post-dose	28.7 (3.3)	39.8 (2.1)		
Change from pre-dose	−12.6 (2.9)	−0.4 (1.3)	0.84	0.001
% change from pre-dose	−30.2 (6.8)	0.1 (3.4)	0.99	0.002

ANCOVA = analysis of covariance; APO = apomorphine; PLB = placebo; SE = standard error; UPDRS = Unified Parkinson's Disease Rating Scale

[a] Primary outcome measure.

[b] *P* value for sequence effect using subject within sequence mean square as the error term.

[c] One-way ANCOVA with the terms pre-dose score and treatment; day 1 data only.
Source: APO 301 Clinical Study Report.[2]

Appendix 5: Validity of Outcome Measures

Aim

To summarize the validity of the following outcome measures:

- diary-recorded “off” time
- Dyskinesia Rating Scale (DRS) — severity of dyskinesia
- hand-tapping test (HTT) score
- Unified Parkinson’s Disease Rating Scale (UPDRS), Part III – motor examination
- Webster step-seconds test (WSST) score.

Findings

Diary-Recorded “Off” Time

The amount of time spent by Parkinson’s disease (PD) patients in the “off” state per day can be measured from patient diaries. One type of diary structure for assessing “off” time in PD patients that has been evaluated is a grid system where patients place a checkmark for each half-hour under the category that best characterizes that period. The categories are typically asleep, “off,” and “on,” often with multiple categories of “on” for indicating severity of dyskinesia.[26,40-42] In the APO 202 study, patients initially recorded the times of onset for “off” and “on” states, and a revision during the trial changed the diary format to the grid system.[1] Sponsor staff converted diary entries previously recorded under the original system to the grid system, and outpatient “off” time per day was calculated from the grid system data.[1]

One study compared two versions of the grid system diary against a reference diary indicating good time and bad time during waking hours in 302 PD patients on levodopa/carbidopa with at least one half-hour of troublesome dyskinesia and one hour of good function every day.[40] The first version of the grid system had “on” categories for absent, mild, moderate, and severe dyskinesia, and 94.3% of “off” time was considered bad time as recorded in 24 diary sets (811 periods).[40] The second version of the grid system had “on” categories for absent, non-troublesome, and troublesome dyskinesia, and 84.9% of “off” time was considered bad time as recorded in 17 diary sets (816 periods).[40] Therefore, patient diary–recorded “off” time is largely considered undesirable by patients. The test-retest reliability of the second version of the grid system was assessed in a separate study of PD patients on levodopa with motor fluctuations and moderately disabling dyskinesias who filled out daily diaries over six days.[42] While “off” time was not assessed, “on” time without dyskinesia or with non-troublesome dyskinesia was found to have acceptable internal consistency (Cronbach’s alpha > 0.7), test-retest reliability (intraclass correlation coefficient or ICC > 0.7), and a moderate strength of correlation with a visual analogue scale characterizing good time (Pearson correlation coefficient = 0.41).[42]

In a study of 472 patients with levodopa-treated PD, diary-recorded mean daily “off” time was compared against both Patient Global Impression of Improvement (PGI-I) and Clinical Global Impression of Improvement (CGI-I) at baseline and week 26.[41] Patient diaries had categories for “on,” “off,” and asleep time.[41] Patients on the trial drug who reported a minimal improvement had a change in mean daily “off” time of −1.9 ± 2.2 hours (n = 69).[41] A CGI-I rating of “minimally improved” was associated with a change in mean daily “off” time of −2.1

± 2.4 hours (n = 74).[41] PGI-I and CGI-I ratings of "no change" in patients on placebo were −0.9 ± 2.5 hours (n = 44) and −0.3 ± 2.7 hours (n = 44).[41] Subtracting the "no change" values in patients on placebo from "minimally improved" values in patients on the trial drug yields minimal clinically important differences (MCIDs) of −1.0 and −1.8 hours using PGI-I and CGI-I as anchors.[41] A similar study testing immediate-release and extended-release versions of pramipexole in a similar sample of PD patients found MCIDs for mean daily "off" time using the same method.[26] The MCIDs found were −1.3 hours for the immediate-release version (n = 55 for drug, n = 43 for placebo) and −1.0 hour for the extended-release version (n = 66).[26]

Dyskinesia Rating Scale

The DRS is a scale developed for assessing dyskinesia based on interference with activities of daily life by modifying the Obeso Dyskinesia Rating Scale.[43] The scale uses three tasks to rate the severity of dyskinesia among patients with PD: walking, putting on a coat, and lifting a cup to the lips for drinking.[43] The tasks were chosen because they involve large and small muscles of all extremities as well as trunk and neck control.[43] Severity of dyskinesia is rated on a 5-point ordinal scale as described below. The type of dyskinesia (chorea, dystonia) and the most disabling type of dyskinesia are also parts of the DRS[43] but were not evaluated in the pivotal studies.

0: Absent
1: Minimal severity, no interference with voluntary motor acts
2: Dyskinesias may impair voluntary movements but patient is normally capable of undertaking most motor acts
3: Intense interference with movement control and daily life activities are greatly limited
4: Violent dyskinesias, incompatible with any normal motor task

The scale developers tested the DRS in a sample of 40 PD patients on chronic dopaminergic therapy with varying types and severities of dyskinesia. Tape recordings of the patients performing the tasks were evaluated by physicians and nurses and each possible rating on the severity scale was represented. Severity of dyskinesia showed acceptable (> 0.7) inter-rater (Kendall's coefficient of concordance W = 0.76 and W = 0.876 for two separate sets of recordings) and intra-rater (Spearman rank correlation coefficient rho = 0.855) reliability.[43] Information on the validity or MCID of the DRS severity of dyskinesia scale was not found.

It should be noted that only studies APO 202 and APO 301 used this form of the DRS severity of dyskinesia scale with the accompanying tasks; in studies APO 302 and APO 303, dyskinesia was rated by clinicians based on general observations on a 4-point scale as follows:

0: Absent
1: Mild
2: Moderate
3: Severe

Hand-Tapping Test

An HTT can be administered to PD patients to measure upper-limb bradykinesia.[44] Patients alternately tap one of two mechanical counting devices mounted on a board 20.3 cm apart from each other.[44] The number of taps counted within 60 seconds for each hand can be summed to give the tapping score.[44] In 10 patients with advanced PD on

levodopa/carbidopa, the HTT score was found in the patients' "off" state and again following levodopa/carbidopa or intranasal apomorphine administration.[44] HTT score significantly increased after levodopa/carbidopa administration (mean change of 117 ± 65 taps) and apomorphine administration (111.8 ± 62 taps).[44] No other information was found for the HTT in PD patients.

A similar technique has been assessed in Huntington's disease patients.[45] In a study with 237 Huntington's disease patients assessed every six or 12 months, patients were asked to alternately tap two buttons 30 cm apart for 30 seconds with each hand.[45] The number of taps declined at a mean rate of 5.1 taps per year (95% confidence interval, 3.8 to 6.3 taps, $P < 0.0001$) and each additional year of age decreased the number of taps by 0.9 (95% confidence interval, 0.4 to 1.4 taps, $P = 0.0007$).[45] The same technique was employed in 178 Huntington's disease patients, and number of taps was negatively associated with Unified Huntington's Disease Rating Scale motor score (Spearman rho = −0.81, $P < 0.0001$), a scale that increases with more severe motor impairment.[46] The number of taps was positively associated with the independence scale (rho = 0.78, $P = 0.01$) for which higher values indicate greater patient independence in daily living activities.[46] In 15 Huntington's disease patients, test-retest reliability over three time points in a day (morning, lunch, and afternoon) was acceptable (> 0.7) as measured by Lin's concordance correlation coefficient (0.90 for morning/noon and 0.96 for noon/afternoon).[46]

Unified Parkinson's Disease Rating Scale (UPDRS), Part III

The UPDRS was created in 1984 and since has been the most widely used method for the evaluation of disability and impairment in PD. The scale is comprised of four parts: Part I (mentation, behaviour, and mood; four items), Part II (activities of daily living; 13 items), Part III (motor examination; 14 items), and Part IV (complications of therapy in past week; 11 items). Individual items in Part III are scored on a 5-point scale (0 to 4) with higher scores indicating worse symptoms. The individual item scores are summed to give a total score ranging from 0 to 56 points.

In patient samples representing patients of various degrees of disability across all stages of the Hoehn and Yahr scale (H&Y), adequate internal consistency (alpha > 0.7) has been demonstrated in the UPDRS-III motor score (alpha ranging from 0.78 to 0.92).[19,21,23] Test-retest reliability of the UPDRS motor score was sufficient in both advanced PD patients on levodopa (ICC = 0.90 in the "off" state and ICC = 0.90 in the "on" state, n = 34)[22] and in early PD patients not on anti-parkinsonian medications (ICC = 0.90, n = 404).[24] Inter-rater reliability was also sufficient in a sample of PD patients, most of whom were on levodopa (ICC = 0.82 for three raters, n = 24).[25]

Content validity of the UPDRS-III was assessed in a sample of patients across all stages of the H&Y scale by surveying a panel of 12 to 13 experts who rated each item on a Likert-type scale ranging from 1 to 4 (not relevant to very relevant).[19] Of the 14 UPDRS-III items, nine had at least 75% of experts assigning a score of 3 or 4.[19] Convergent validity was assessed to establish construct validity of the UPDRS-III motor score.[19,21,26] The UPDRS motor score is positively associated with the H&Y and modified H&Y scales (Spearman rho = 0.87, n = 59; rho = 0.62, $P < 0.001$, n = 1,136)[19,23] and negatively associated with the Schwab and England Activities of Daily Living scale (rho = −0.87, n = 59; rho = −0.69, $P < 0.001$, n = 1,136).[19,23]

Several estimates of an MCID for the UPDRS motor score have been made, with variation from the method of estimation (anchor-based or distribution-based), patient population (early

PD, advanced PD, or mixed), and intervention (Table 24).[18,20,26] Estimates of MCID provided in the table for advanced PD may not pertain to measurements in the "off" state.

Table 24: Summary of MCID Findings for UPDRS-III Motor Score

Study Author, Year	Patient Characteristics	Measurement	MCID for UPDRS-III Motor Score
Hauser et al. (2014)[26]	• 517 patients with advanced, levodopa-treated PD • Trial with pramipexole IR and ER	• Mean change in UPDRS-III score from baseline to 18 weeks • MCID = mean change in UPDRS-III for treated patients with PGI-I "minimal change" minus mean change in UPDRS for placebo patients with PGI-I "no change"	• Pramipexole ER MCID: −5.2 points • Pramipexole IR MCID: −6.5 points
Schrag et al. (2006)[20]	• 603 patients with early PD and H&Y stage of 1 to 3 • Two trials with ropinirole	• Mean change in UPDRS-III score from baseline to 24 weeks for: ○ CGI-I "minimally improved" ○ CGI-I "no change" to assess placebo effect • Cohen's effect size of UPDRS-III score from baseline to 24 weeks	Mean change in UPDRS-III for CGI-I "minimally improved": • Study 1: −5.0 points, n = 83 • Study 2: −5.3 points, n = 72 Effect size for mean change in UPDRS-III: • "Minimally improved": −0.5 (medium)
Shulman et al. (2010)[18]	• 653 patients with PD of all stages of the modified H&Y scale • Two trials with dopamine agonist	• Distribution-based analysis: Cohen's effect sizes for UPDRS-III score (0.2 for minimal, 0.5 for moderate, and 0.8 for large) • Anchor-based analysis: ○ 4-point and 10-point changes in SF-12 PH and SF-12 MH are minimal and moderate effect, respectively ○ SF-12 MH ○ 10% change in S&E scale is a moderate effect ○ 1-point change in H&Y stage is a large effect	Mean effect sizes for UPDRS-III score from all methods: • Minimal: 2.5 points • Moderate: 5.2 points • Large: 10.8 points

CGI-I = Clinical Global Impression of Improvement; ER = extended release; H&Y = Hoehn and Yahr; IR = immediate release; MCID = minimal clinically important difference; MH = mental health; PD = Parkinson's disease; PGI-I = Patient Global Impression of Improvement; PH = physical health; S&E = Schwab and England; SF-12 = 12-point Short Form Health Status Survey; UPDRS = Unified Parkinson's Disease Rating Scale.

Three studies assessed MCIDs for UPDRS-III score using data from trials for dopamine agonists.[18,20,26] One study in early PD patients reported decreases of 5.0 points and 5.3 points as corresponding to minimal improvement in the CGI-I,[20] while another study in PD patients of all H&Y stages reported a moderate effect size of −5.2 points.[18] Another study in advanced PD patients on levodopa found similar results with PGI-I, even after taking potential placebo effect into account for the two versions of the trial drug (−5.2 points and −6.5 points).[26]

Webster Step-Seconds Test

The WSST score is meant to be a simple method of measuring overall disability from gait disturbance in PD patients.[28] The number of seconds it takes for the patient to rise from a sitting position, walk 15 feet, turn around, walk back to the chair, turn around, and sit back down is recorded by an observer.[28] The number of steps the right leg makes is also recorded, and the two values are multiplied to give the step-seconds score.[28] If a patient

cannot rise from the seated position, this can be noted and help can be provided for the test.[28] Typical scores are presented by the developer, though evidence for these ranges is not provided[28]:

- Normal persons: 50 to 100 step-seconds
- Early PD with mild slowing and shortening of stride during turnaround: 100 to 200 step-seconds
- Moderately advanced PD with sustained shortening of stride: 200 to 400 step-seconds
- Far-advanced PD: greater than 400 step-seconds

Principal component analysis in a battery of 13 different instruments for assessing disability in PD suggested that a modified step-seconds score (10 metres distance instead of 15 feet) and the Purdue-pegboard test for finger dexterity measure related constructs.[47] However, no information on validity, reliability, or MCID was found for the WSST score.

Table 25: Validity and Minimal Clinically Important Differences of Outcome Measures

Instrument	Type	Evidence of Validity	MCID	References
Diary-recorded "off" Time	Mean daily hours spent in "off" state as recorded by patients in a diary	Limited	−1.0 to −1.8 hours	Hauser et al. (2000),[40] Hauser et al. (2011),[41] Hauser et al. (2014)[26]
Dyskinesia Rating Scale — severity of dyskinesia	A set of 3 tasks to measure severity of dyskinesia in PD with each item scored on a 5-point ordinal scale	Limited	Unknown	Goetz et al. (1994)[43]
Hand-tapping test score	A measure of upper-limb bradykinesia based on a repetitive tapping task performed within a set amount of time	Limited	Unknown	Dewey et al. (1996),[44] Michell et al. (2008),[46] Collins et al. (2014)[45]
UPDRS-III motor examination	A set of 14 tasks to measure disability and impairment in PD with each item scored on a 4-point Likert-type scale	Yes	−5.0 to −6.5 points	Hauser et al. (2014),[26] Schrag et al. (2006),[20] Shulman et al. (2010)[18]
Webster step-seconds test score	A measure of gait disturbance in PD that is the product of the number of seconds and the steps it takes to perform a walking task	No	Unknown	Webster 1968,[28] Baas et al. (1993)[47]

MCID = minimal clinically important difference; PD = Parkinson's disease; UPDRS = Unified Parkinson's Disease Rating Scale.

Conclusions

Several approaches are available to evaluate motor function and fluctuations in patients with PD. Out of the outcomes described in this appendix, the UPDRS motor score is the only outcome for which validity (content and construct validity), reliability (internal consistency, inter-rater reliability, and intra-rater or test-retest reliability), and MCID information in PD patients were found. It is one part of a four-part instrument that evaluates disability and impairment in PD and has an estimated MCID of a 5-point to 6.5-point decrease. The remaining outcomes have been only partially evaluated for validity and reliability and an MCID is unavailable except for "off" time. "Off" time recorded in half-hour periods by patients in diaries coincides with what patients consider to be bad time, and it has an approximate

MCID of a 1-hour to 1.8-hour per day decrease. Severity of Dyskinesia, a part of the Goetz Dyskinesia Rating Scale, examines interference of dyskinesia with daily activities of living and has acceptable inter-rater and intra-rater reliability. General observations made by clinicians in the absence of the tasks specified in the Goetz scale were used to score dyskinesia in studies APO 302 and APO 303, and this method should not be mistaken for the Goetz version. HTT score, a measure of upper-limb bradykinesia, has been shown to change in PD patients following levodopa or apomorphine administration. Construct validity and test-retest reliability have been demonstrated for HTT score in Huntington's disease patients, but not in PD patients. Finally, no information on validity, reliability, or MCID was found for the WSST score.

Appendix 6: Summary of the APO 303 and APO 401 Studies

Aim

The aim of this appendix is to provide a summary and critical appraisal of the two long-term safety trials, APO 303 and APO 401.

Background

The manufacturer-provided clinical study reports on two studies, APO 303 and APO 401, designed to assess the long-term safety of intermittent subcutaneous apomorphine for the treatment of refractory "off" episodes in Parkinson's disease (PD) patients already on optimized oral levodopa/carbidopa and dopamine agonists. These two studies were considered supportive by Health Canada and mainly provided information on hypotension and electrocardiogram parameters during forced titration (APO 303) and long-term outpatient use (APO 401).[4] The studies were not included in the CADTH Common Drug Review main report because maximum individual and daily dosages of apomorphine in the studies exceeded the product monograph–recommended dose. The details of the studies are summarized in Table 26.

Table 26: Details of Included Studies

		APO 303	APO 401
	Aim/Objective	A dose-escalation substudy of APO 401 to assess the efficacy and safety of SC APO to treat "off" episodes in APO-naive patients with late-stage PD	To assess the long-term safety and AE profile of outpatient, intermittent, SC use of APO to treat "off" periods in patients with advanced PD
Designs and Populations	**Study Design**	Three parts: 1. Open-label dose-escalation phase 2. Randomized, placebo-controlled, double-blind crossover phase (2 visits within the dose-escalation phase) 3. Open-label outpatient phase	Two parts: 1. Open-label in-office dose-titration phase 2. Open-label ≥ 1-year outpatient phase
	Locations	17 centres in the US	61 centres in the US
	Randomized (N)	51, but only during the crossover period	No
	Inclusion Criteria	• Age ≥ 18 years • Idiopathic PD • H&Y stages 2 to 5 (assessed during patient's "on" state) • Experiencing refractory motor fluctuations • Receiving optimally maximized levodopa/carbidopa and an oral dopaminergic agonist for ≥ 30 days (unless intolerant to dopamine agonists) • Patients enrolled in APO 401 who have completed initial baseline observations, but have not received APO therapy as part of the APO 401 protocol or at any other point in time	Same as in APO 303, with the addition of the following: • Patient or caregiver had to be able to recognize an "off" state and be sufficiently motivated to learn how to use APO injection to control these periods • Patient or caregiver had to be able to maintain "on/off" diaries
	Exclusion Criteria	• Prior APO use • Medical therapy for clinically significant psychoses or dementia	Same as APO 303, except for prior APO use. Patients were excluded if their APO regimen did not use intermittent SC injection.

		APO 303	APO 401
		• History of drug or alcohol dependency within one year prior to study enrolment • Unstable and clinically significant disease of cardiovascular, hematologic, hepatic, renal, metabolic, respiratory, gastrointestinal, or endocrinological systems, or neoplasm within 3 months before the start of the study • Methyldopa therapy • Allergies to morphine derivatives, sulphur drugs, trimethobenzamide, or anticholinergics • Other experimental drugs within 30 days before study entry	
Drugs	**Intervention**	APO 10 mg/mL administered SC and intermittently. Patients were strongly encouraged to begin antiemetic therapy at least three days before APO dosing (trimethobenzamide hydrochloride, TMB 250 mg 3 times daily) and continue it for ≥ 6 weeks after starting APO. Three parts (see Study Design): 1. Dose escalation starting at 2 mg at titration visit 1 followed by increments of 2 mg on separate treatment visits until prevented by intolerable side effects 2. 4 mg single dose of APO or placebo at titration visits 2 and 3 in a crossover fashion 3. The dose with the best balance of beneficial and adverse effects was selected for the outpatient phase, with adjustments as necessary. The maximum individual dose allowed was 10 mg with a total daily maximum of 10 injections and maximum daily dose of 100 mg. Patients and caregivers were allowed to adjust the dose by up to 2 mg during the outpatient phase. Each titration visit occurred within 3 days of the preceding visit. Response to APO was evaluated during the first observed “off” event occurring at least 1 hour after administration of the normal morning dose of oral anti-PD medication.	APO 10 mg/mL administered SC and intermittently. Patients were strongly encouraged to begin antiemetic therapy at least three days before APO dosing (TMB, 250 mg 3 times daily) and continue it for ≥ 6 weeks after starting APO. Titration of APO dose, starting with 2 mg, to the maximum allowed dose effective in reversing muscular dysfunction without unacceptable AEs APO could be administered at any time in response to the onset of “off” events, with dose adjustments as necessary. The maximum individual dose allowed was 10 mg with a total daily maximum of 10 injections and maximum daily dose of 100 mg.
	Comparator(s)	During part 2: volume-matched placebo (pH-matched vehicle) injection given randomly at titration visit 2 or 3 only, in a DB crossover manner	No comparators
Duration	**Baseline and Titration Visits**	< 1 month, consisting of 1 baseline visit and up to 6 titration visits at ≤ 3-day intervals	1 month, consisting of 2 baseline visits and dose adjustment visits as necessary
	Double-Blind Crossover	Titration visits 2 and 3, scheduled within 3 days of each other.	NA
	Follow-Up / Outpatient Visits	6 months with in-office evaluation visits at 1 week, 2 weeks, and 1, 4, and 6 months	1 year, with the option of treatment extension Routine visits at 1 month after initial dosing followed by routine visits at 4-month intervals

		APO 303	APO 401
Outcomes	**Primary End Point**	Primary end point: change in UPDRS motor score from pre-dose to 20 minutes post-dose during the DB crossover period	No primary efficacy end points analyzed
	Other End Points	• Change in UPDRS motor score from pre-dose to 40 and 90 minutes post-dose • AUC for UPDRS motor scores at 0, 20, 40, and 90 minutes • Change in dyskinesia from pre-dose to 20, 40, and 90 minutes post-dose	• H&Y scale • UPDRS score (total, motor exam, non-motor exam, and complications of therapy) • Number and duration of "off" episodes, number of daily injections, and length of time from injection to "on" based on available diary entries

	Safety End Points	• Blood pressure and 7-lead Holter monitoring at baseline (pre-dose) and 20, 40, and 90 minutes post-dose
		• Orthostatic hypotension
		  ○ Criterion 1: a drop of ≥ 20 mm Hg in SBP or ≥ 10 mm Hg in DBP
		  ○ Criterion 2: a drop of ≥ 30 mm Hg in SBP with a standing value ≤ 90 mm Hg, or a ≥ 20 mm Hg drop in DBP with a standing value ≤ 50 mm Hg
		• Corrected QT interval measured with Holter monitoring during the dose-titration phase
		• AEs
			• Orthostatic hypotension
			  ○ Criterion 1: a drop of ≥ 20 mm Hg in SBP or ≥ 10 mm Hg in DBP
			  ○ Criterion 2: a drop of ≥ 30 mm Hg in SBP with a standing value ≤ 90 mm Hg, or a ≥ 30 mm Hg drop in DBP with a standing value ≤ 50 mm Hg
			• Change from baseline visit 1 in PR, QRS, QT, and corrected QT intervals at routine visits measured with 12-lead ECG
			• AEs

	Other Safety Assessments	• Vital signs • Clinical laboratory testing: hematology, serum chemistry, urinalysis, and pregnancy test	Same as in APO 303
Notes	**Publications**	Pahwa et al. (2007)[30]	LeWitt et al. (2009)[10]

AE = adverse event; APO = apomorphine hydrochloride; AUC = area under the curve; CSR = Clinical Study Report; DB = double-blind; DBP = diastolic blood pressure; ECG = electrocardiogram; H&Y = Hoehn and Yahr; NA = not applicable; PD = Parkinson's disease; QT = QT interval; SBP = systolic blood pressure; SC = subcutaneous; TMB = trimethobenzamide; UPDRS = Unified Parkinson's Disease Rating Scale.

Note: Oral dopaminergic agonist refers to bromocriptine, pergolide, ropinirole, or pramipexole.

Source: APO 303,[30] APO 303 CSR,[48] APO 401,[10] APO 401 CSR.[15]

Included Studies

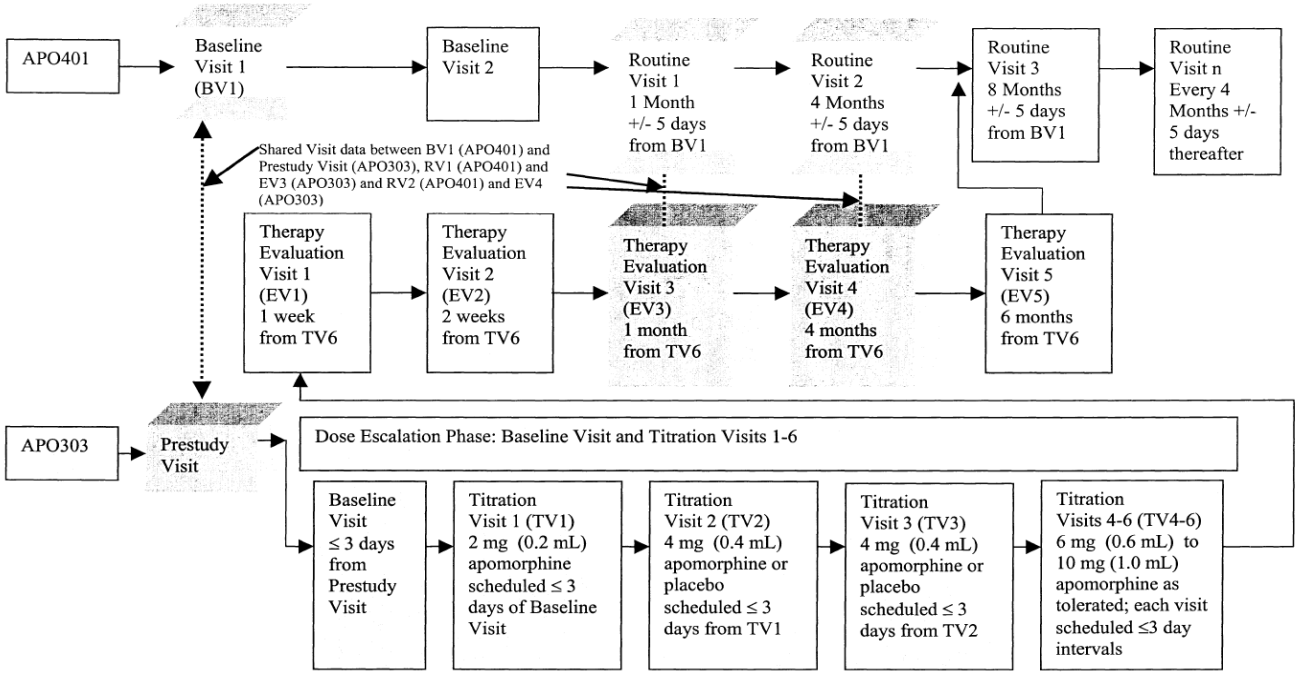
Description of Studies

APO 401 was a large-scale safety trial conducted to assess the long-term safety profile of continued use of intermittent subcutaneous apomorphine to treat refractory "off" episodes in patients with already receiving an optimized regimen of levodopa and an oral dopamine agonist. This was an open-label trial consisting of two phases: an in-office phase consisting of a baseline assessment (baseline visit 1) and dose-titration visit (baseline visit 2), and an outpatient open-label treatment phase. The follow-up period was at least one year, and patients could renew treatment for longer periods. During the baseline and dose-titration period, some patients were recruited for the APO 303 trial, and the six-month outpatient follow-up period in APO 303 coincided within the one-year outpatient follow-up duration in APO 401. APO 401 was conducted in 61 sites in the US from July 1999 to July 2005, and a total of 546 patients received at least one apomorphine dose. Figure shows the interrelationship between the APO 303 and APO 401 trials. Since the provided clinical study

report[11] is an interim report, the results in the present report are from the corresponding published article.[10]

The primary objective of APO 303 was to evaluate the electrocardiographic and orthostatic effects of intermittent subcutaneous apomorphine in apomorphine-naive PD patients. The study was divided into three phases: an in-patient open-label dose-titration phase; a randomized, placebo-controlled, double-blind crossover phase over two titration visits with a fixed apomorphine dose of 4 mg; and a six-month open-label treatment phase with the option of further continuing apomorphine treatment as part of the APO 401 trial. In total, 56 patients originally enrolled in the APO 401 trial were recruited for this study between February 2001 and August 2002 at 17 US centres.

Figure 5: Flow Chart of 401 (A) and APO 303 (B)



Source: APO 303 Clinical Study Report.[48]

Populations

Patients who participated in the APO 401 trial were assessed for inclusion in the APO 303 substudy during the APO 401 baseline visit. Therefore, the inclusion and exclusion criteria in both studies were essentially the same, with the exception of apomorphine-naive patients for the APO 303 trial. The APO 401 trial granted 46 patients waivers to enroll without meeting all the inclusion and exclusion criteria. Most waivers were for patients in whom dopamine agonists were intolerable or ineffective.

There were higher proportions of males and whites in both trials. The baseline characteristics in the crossover groups in the APO 303 trial appeared to be balanced. Patients in both trials were around 66 years on average, had a mean Unified Parkinson's Disease Rating Scale (UPDRS) total score around 55, had a range of Hoehn and Yahr

(H&Y) stages of 1 to 5, and were on optimized anti-PD medications. The baseline characteristics of patients in both trials are given Table 27.

Table 27: Summary of Baseline Characteristics

Characteristics	APO 303				APO 401
	In-Office Population, N = 56	Crossover Population, N = 51		Outpatient Population, N = 51	N = 546
		PLB/APO, n = 25	APO/PLB, n = 26		
Demographics					
Male, n (%)	33 (59)	14 (56)	16 (62)	31 (61)	360 (66)
Female, n (%)	23 (41)	11 (44)	10 (38)	20 (39)	186 (33)
White, n (%)	52 (93)	23 (92)	24 (92)	47 (92)	NR
Hispanic, n (%)	3 (5)	2 (8)	1 (4)	3 (6)	NR
Mean age, years (SE)	66.6 (1.2)	66.2 (1.8)	66.7 (1.7)	66.1 (1.3)	65.2 (0.4)
Tobacco Use, n (%)					NR
None	33 (59)	15 (60)	16 (62)	31 (61)	NR
Former (> 1 year)	21 (38)	9 (36)	10 (38)	19 (37)	NR
Current	2 (4)	1 (4)	0	1 (2)	NR
Alcohol Use, n (%)					
None	48 (86)	21(84)	24 (92)	45 (88)	NR
Moderate	8 (14)	4 (16)	2 (8)	6 (12)	NR
PD Characteristics, n	n = 54	n = 24	n = 25	n = 49	
Mean age of onset, years (SE)	55.2 (1.3)	55.6 (1.9)	54.8 (2.0)	54.8 (1.4)	54.0 (0.5)
Mean UPDRS total score (SE)[a]	55.7 (3.3)	52.8 (5.23)	60.8 (4.6)	56.0 (3.5)	54.6 (1.0)
Mean UPDRS motor score (SE)[a]	28.9 (2.3)	27.5 (3.8)	31.2 (3.3)	29.2 (2.5)	NR
Mean UPDRS non-motor score (SE)[a]	27.4 (1.4)	26.5 (2.3)	29.6 (1.9)	27.4 (1.4)	NR
H&Y stage, 1 to 5, n (%)					
1	NR	NR	NR	NR	2 (0.4)
2	NR	NR	NR	NR	142 (26)
3	NR	NR	NR	NR	266 (49)
4	NR	NR	NR	NR	119 (22)
5	NR	NR	NR	NR	14 (3)
Pattern of “off” episodes, n (%)					
“On/off”	NR	NR	NR	NR	80 (15)
“Wearing off”	NR	NR	NR	NR	163 (30)
Both	NR	NR	NR	NR	303 (56)
Background Anti-PD Medications,[b] %					

Characteristics	APO 303				APO 401
	In-Office Population, N = 56	Crossover Population, N = 51		Outpatient Population, N = 51	N = 546
		PLB/APO, n = 25	APO/PLB, n = 26		
Carbidopa/levodopa	100				
Entacapone (200 mg/day to 1,800 mg/day)	48				
Pramipexole (0.75 mg/day to 6 mg/day)	32				
Amantadine (100 mg/day to 400 mg/day)	25				
Pergolide (0.75 mg/day to 4 mg/day)	21				
Selegiline (5 mg/day to 10 mg/day)	18				
Ropinirole (0.75 mg/day to 15 mg/day)	16				
Bromocriptine (33.75 mg/day to 60 mg/day)	4				
Diphenhydramine (25 mg/day to 125 mg/day)	4				
Tolcapone (300 mg/day to 600 mg/day)	5				
Trihexyphenidyl (3 mg/day to 6 mg/day)	4				
Clonazepam (1.5 mg/day)	2				
Concomitant Illness, n					
Postural/orthostatic hypotension history	9	-	-	-	29
Stroke/TIA history	-	-	-	-	12
Hematological disorders	-	-	-	-	43
Concomitant Non-PD Medications, n (%)					
Anti-hypertensive	8 (14)	-	-	-	NR
Vasodilators	7 (13)	-	-	-	NR
Beta-blocker	3 (5)	-	-	-	NR

APO = apomorphine; CSR = Clinical Study Report; H&Y = Hoehn and Yahr; NR = not reported; PD = Parkinson's disease; PLB = placebo; SE = standard error; TIA = transient ischemic attack; UPDRS = Unified Parkinson's Disease Rating Scale.

[a] For APO 303, assessments were made during the "on" period. If assessment could not be made while patient was "on," it was discarded. For APO 401, assessments were conducted in "on" state for 457 patients and in "off" state for 86 patients.

[b] Background anti-PD medications were taken throughout the duration of the study, regardless of treatment and in-patient or outpatient status.

Source: APO 303,[30] APO 303 CSR,[48] APO 401,[10] APO 401 CSR.[15]

Interventions

In APO 303, apomorphine 10 mg/mL and pH-matched placebo were supplied in identical 2 mL ampoules and blinded cartons during crossover visits and unblinded cartons for all other visits. The response to treatment with a single dose of apomorphine during the in-patient phase was evaluated at the first observed "off" episode throughout the dose-titration visits. The dose started at 2 mg (0.2 mL) and increased by 2 mg in each subsequent visit up to a maximum dose of 10 mg (1 mL), or lower based on tolerability. At the 4 mg dose level (dose-titration visits 2 and 3), either 4 mg apomorphine or volume and placebo were given in a randomized, double-blind, crossover fashion. The optimal apomorphine dose determined during the in-patient phase was the initial dose used in the outpatient phase. Patients or

caregivers administered the optimal dose of apomorphine for six months in the outpatient phase in response to “off” episodes. The dose could be adjusted by 2 mg, with a maximum of 10 mg per injection and 10 injections per day.

In APO 401, patients received apomorphine 10 mg/mL in ampoules, membrane-puncture vials, pre-filled syringes, or an injector pen with pre-filled cartridges. For patients not enrolled in APO 303, two basic dose-titration schemes were used in the first phase, starting with the first dose of 2 mg during baseline visit 2. Doses were increased incrementally until optimal relief of motor dysfunction occurred or adverse events (AEs) exceeded beneficial effects. Increased doses were administered either on subsequent days or during baseline visit 2 following an inadequate response within 20 minutes of the previous dose. Up to five injections were administered during titration. For the outpatient phase, patients were allowed to adjust apomorphine dose at 1 mg (2 mg with investigator contact) intervals and patients could receive a dose adjustment visit at any point in the study as necessary. As in APO 303, the maximum dose per injection and number of injections per day were 10 mg and 10 injections.

Based on patient diaries during the outpatient phase in APO 401, the mean dose and number of injections was 4 mg three times a day, with a mean increase from baseline dose of 0.86 mg after 12 months. More than 75% of the patients used apomorphine at least once daily, and more than 85% used apomorphine at least three times a week. Patients did not necessarily use apomorphine to treat every “off” event, though data for this were not reported. Almost all patients took the antiemetic trimethobenzamide, with 55% of the 546 patients discontinuing its use at some point during the study and 41% of patients continuing to use it regularly. During the dose-escalation phase of APO 303, most of the patients reached a maximum single dose consistent with the product monograph of 6 mg or less (85% of the intention-to-treat set and 79% of the safety set).

Outcomes

The primary efficacy end point in APO 303 was the change in UPDRS-III motor score from pre-dose to 20 minutes post-dose. The primary efficacy end point was measured during both visits of the double-blind crossover period and compared between the apomorphine (4 mg) and placebo treatments. Exploratory analyses were conducted for the change in UPDRS-III motor score at 40 and 90 minutes post-dose and the area under the curve for UPDRS-III motor score using measurements at 0, 20, 40, and 90 minutes post-dose. Change in UPDRS-III was also assessed at the same time intervals during the outpatient visits. Change in the severity of dyskinesia from pre-dose to 20, 40, and 90 minutes post-dose was also part of the exploratory analysis. Clinicians rated dyskinesia on an ordinal 4-point scale ranging from absent (0 points) to severe (3 points) based on general observation of patients. Safety outcomes in both trials included AEs, orthostatic hypotension, electrocardiogram abnormalities, vital signs, and clinical laboratory testing. Blood pressure was measured after five minutes in the sitting (in APO 303) or supine (in APO 401) position and at two minutes after being brought to the standing position. To meet the definition of orthostatic hypotension (criterion 1), a patient had to experience a systolic blood pressure (SBP) drop of at least 20 mm Hg or a diastolic blood pressure (DBP) drop of at least 10 mm Hg. A stricter definition (criterion 2) was also assessed (see Table 26). Symptomatic hypotension, described as lightheadedness or dizziness upon standing, was reported by patients as an AE.

Table 28: Patient Disposition

APO 303		APO 401	
Enrolled, N	56		
Randomized, n (%)	51 (91)		
Completed crossover period, n (%)	50 (89)	Received ≥ 1 dose of APO, N	546
Completed in-office phase up to TV6, n (%)	14 (25)		
Completed crossover period, proceeded to outpatient phase, n (%)	36 (64)	Received APO in outpatient phase, n (%)	535 (98)
Proceeded to outpatient phase before end of crossover period, n (%)	1 (2)		
Proceeded to outpatient phase following TV3 (4 mg dose), n (%)	6 (11)		
Proceeded to outpatient phase following TV4 (6 mg dose), n (%)	19 (34)		
Proceeded to outpatient phase following TV5 (8 mg dose), n (%)	11 (20)		
Proceeded to outpatient phase following TV6 (10 mg dose), n (%)	13 (23)		
Completed 6-month outpatient phase, n (%)	33 (59)	Completed at least 12-month follow-up, n (%)	296 (54)
Discontinuation, n (%)	23 (41)	**Discontinuation, n (%)**	424 (78)
WDAEs, n (%)	17 (30)	WDAEs, n (%)	187 (34)
Early termination and not lost to follow-up, n (%)	3 (5)	Early termination or lost to follow-up, n (%)	155 (28)
Unsatisfactory response, n (%)	1	Unsatisfactory response, n (%)	48 (9)
Lost to follow-up, n (%)	2	Lost to follow-up without declared study termination, n (%)	31 (6)

APO = apomorphine; CSR = Clinical Study Report; TV = titration visit; WDAE = withdrawal due to adverse event.

Source: APO 303,[30] APO 303 CSR,[48] APO 401,[10] APO 401 CSR.[15]

Table 29: Exposure to Study Treatment

APO 303		APO 401	
APO Dose Reached During Titration Visits, n		**Exposure During Outpatient Phase**	
2 mg	56	Mean final dose, mg	3.43
4 mg	51	Median final dose, mg (range)	3.0 (0.5 to 10.0)
6 mg	44	Mean duration of study, days	578.8
8 mg	25	Mean dose based on patient diaries, mg	4
10 mg	14	Mean number of injections per day based on patient diaries, n	3

APO = apomorphine hydrochloride; CSR = Clinical Study Report.

Source: APO 303,[30] APO 303 CSR,[48] APO 401,[10] APO 401 CSR.[15]

Table 30: Statistical Analyses in APO 303

	APO 303
Sample Size and Power	• Change in UPDRS score for the crossover period only was used for sample size calculation. • Based on the APO 202 and 301 studies, mean UPDRS-III score changes of −5 (SD = 14) for PLB and −20 (SD = 14) for APO were estimated. • A sample size of 25 patients in each group was estimated to provide 96% power to detect a difference of 15 in UPDRS score between the groups at alpha = 0.05.
Efficacy Analysis (ITT Population)	• Change in UPDRS motor score analyzed using repeated-measures ANCOVA[a] or Wilcoxon rank sum test with alpha = 0.05.
	• Change in UPDRS motor score and AUC from pre-dose up to 90 minutes post-dose analyzed using the same ANCOVA[a] model with alpha = 0.05. LOCF method used to impute missing data.
	• Change in dyskinesia assessed using Wilcoxon rank sum test with alpha = 0.05.
Safety Analysis (ITT Population)	• Change in BP and HR analyzed using repeated-measures ANOVA.
	• Incidence of AEs measured using McNemar's test, summarized by severity, duration, action taken, outcome, and treatment status.
	• Change in BP measured using McNemar's test.
	• Change in Holter monitoring measured using repeated-measures ANCOVA.[a]

AE = adverse event; ANCOVA = analysis of covariance; ANOVA = analysis of variance; APO = apomorphine; AUC = area under the curve; BP = blood pressure; CSR = Clinical Study Report; HR = heart rate; ITT = intention-to-treat; LOCF = last observation carried forward; PLB = placebo; SD = standard deviation; UPDRS = Unified Parkinson's Disease Rating Scale.

[a] ANCOVA model with the terms sequence, subject within sequence, pre-dose score, treatment, and period.

Source: APO 303,[30] APO 303 CSR,[48] APO 401,[10] APO 401 CSR.[15]

Table 31: Analysis Populations

Population	APO 303	APO 401
ITT	All qualifying patients who were randomized and completed the initial crossover visit (TV2), N = 51	–
PP	All patients who completed the DB crossover period (TV2 and TV3), N = 50	–
Safety	Same as ITT, N = 56	N = 546

CSR = Clinical Study Report; DB = double-blind; ITT = intention-to-treat; PP = per-protocol; TV = titration visit.

Source: APO 303,[30] APO 303 CSR,[48] APO 401,[10] APO 401 CSR.[15]

Results

Efficacy Results

During the crossover phase, mean change in UPDRS-III motor score showed statistically significant reduction in the apomorphine 4 mg group compared with placebo from pre-dose to 20 minutes (primary efficacy end point: −11.2 versus −2.8; $P = 0.0002$), 40 minutes (−13.5 versus −3.0; $P < 0.0001$), and 90 minutes (−5.1 versus −1.6; $P = 0.02$) post-dose according to analysis of covariance (ANCOVA) analysis. Sensitivity analyses were conducted for the primary end point, UPDRS-III motor score change at 20 minutes. The primary end point showed a statistically significant reduction with apomorphine treatment when evaluated with the Wilcoxon rank sum test ($P = 0.0001$) due to departures from normality. Further analysis using only dose-titration visit 2 data due to significant sequence effect ($P = 0.0166$) also showed a reduction in UPDRS score at 20 minutes post-dose with apomorphine treatment ($P = 0.02$). The case study report for APO 303[48] stated that there was no significant

carryover effect from apomorphine treatment on the placebo response, though evidence for this was not presented.

The mean change from baseline area under the curve for UPDRS-III motor score was statistically significantly greater for apomorphine 4 mg compared with placebo (−825 versus −199; $P < 0.0001$). However, analysis of only dose-titration visit 2 data due to sequence effects did not show a significant difference between the groups ($P = 0.08$). Subjective assessment of dyskinesia on a 4-point ordinal scale showed an increase in the incidence of dyskinesia in the crossover population following apomorphine injection at all time points (*P* values from 0.01 to 0.03). During the outpatient phase, mean change in UPDRS motor score was assessed during visits from one week to six months after the dose-escalation phase. There was no placebo comparison, and the decrease in UPDRS motor score from pre-dose to 20 and 40 minutes post-dose ranged from 10.5 to 15.3 points.

Safety Results

Safety analyses in APO 303 were exploratory, and *P* values are reported for descriptive purposes only. Assessment of blood pressure in both sitting and standing positions indicated greater mean decrease in SBP and DBP with apomorphine 4 mg compared with placebo at all time points. The greatest reduction was seen for sitting and standing SBP at 20 minutes post-dose (−8.0 mm Hg versus −0.6 mm Hg and −8.7 mm Hg versus 1.2 mm Hg, respectively) and 40 minutes (−6.8 mm Hg versus 0.1 mm Hg and −7.7 mm Hg versus 1.4 mm Hg, respectively). The number of patients who experienced orthostatic hypotension (based on criterion 1 or criterion 2) was not significantly different between apomorphine 4 mg and placebo during the crossover phase. However, symptomatic hypotension in the crossover phase was shown to be more common with apomorphine treatment than with placebo at 20 minutes (17.6% versus 7.8%) and 40 minutes (11.8% versus 2.0%) post-dose.

All but one patient in APO 303 reported at least one AE (98.2%), and four patients experienced at least one serious AE (SAE) (7.1%). During the crossover phase, the proportion of visits during which AEs occurred was greater with apomorphine treatment compared with placebo at 20 and 40 minutes post-dose ($P = 0.0001$ and $P = 0.0002$). Most AEs were mild to moderate in intensity and were considered definitely, probably, or possibly related to apomorphine treatment. These AEs included nausea, vomiting, injection site reactions, fatigue, dizziness, dyskinesias, sedation, sweating, and yawning. Only one SAE, syncope and sinus arrest, was considered related to study treatment, and the patient recovered within two minutes of the event.

In the APO 401 trial, 509 of 546 patients experienced at least one AE (93.2%); all AEs were mild to moderate in nature. AEs resulted in study discontinuation in 187 patients (34%). Forty-five deaths were registered during the study, none of which was related to study treatment. Other AEs resulting in treatment discontinuation were well-known side effects of apomorphine, including nausea or vomiting, dyskinesia, sedation, somnolence, lethargy, and injection site reactions.

A total of 199 patients (36%) in the APO 401 trial reported the occurrence of SAEs. With the exception of 19 patients experiencing 27 SAEs, most were considered remotely or definitely not related to the study drug. The most common SAEs that were considered possibly or probably related to apomorphine included three instances of syncope and drug-induced psychosis each, two instances of postural hypotension and falls each, and one instance in each of atrial flutter, atrial fibrillation, bradycardia (not otherwise specified), breast cancer (in

a female patient), confusion, congestive cardiac failure, depressed level of consciousness, dysarthria, worsening dyskinesias, hallucinations, hypotension, lethargy, mood disorder (not otherwise specified), musculoskeletal pain, personality change, aggravation of psychosis, and cardiac sinus arrest.

Notably among the AEs in APO 401, there was an increase in the frequency of orthostatic hypotension pre-apomorphine and post-apomorphine dosing during both the dose-titration visits (14% versus 23.4% of patients, respectively) and subsequent outpatient treatment evaluation visits (23.3% versus 27.5%, respectively) according to criterion 1 in Table 26. Baseline incidence of orthostatic hypotension defined by criterion 1 before initiation of apomorphine therapy was estimated at 19%. The majority (87%) of the orthostatic hypotension events were asymptomatic.

The frequencies of patient-reported dyskinesia and nausea based on patient diaries were 78% and 39%, respectively. On a scale of 1 (mild) to 3 (severe), the mean severity scores for both outcomes were 0.61 and 0.12 for dyskinesia and nausea. A mean score of at least 2 (moderate) was found for three patients experiencing nausea and 15 patients experiencing dyskinesia. Of the 34 patients who did not receive a dopaminergic agonist, 18 (53%) had at least one episode of nausea or vomiting as opposed to 36% of patients who were receiving a dopaminergic agonist.

Table 32 summarizes the AEs found among the APO 303 and APO 401 patients at a frequency of 10% or higher.

Table 32: Summary of Treatment-Emergent AEs

Event	Patients, n (%)		Relatedness With Treatment, n					
			Definite		Probable		Possible	
	APO 303	APO 401	APO 303	APO 401	APO 303	APO 401	APO 303	APO 401
Any AE	55 (98)	509 (93)	–	–	–	–	–	–
SAEs	4 (7)	199 (36)	–	–	–	–	–	–
Death	1 (2)	45 (8)	–	–	–	–	–	–
AEs Occurring in > 10% of Patients								
PD aggravated	–	69 (13)	–	0	–	1	–	6
Any infection	11 (20)	–	0	–	0	–	0	–
Arthralgia	–	76 (14)	–	1	–	0	–	0
Back pain	–	59 (11)	–	0	–	1	–	0
Depression	–	71 (13)	–	0	–	0	–	8
Dizziness	21 (38)	118 (22)	6	24	7	31	5	37
Dyskinesia	20 (36)	130 (24)	7	30	5	42	5	33
Ecchymosis	6 (11)	57 (10)	1	5	1	2	0	2
Fall	16 (29)	181 (33)	0	0	0	1	2	26
Fatigue	8 (14)	–	1	–	2	–	3	–
Hallucination	6 (11)	104 (19)	0	3	0	9	3	39
Headache	11 (20)	57 (10)	1	1	2	12	3	14
Injection site bruising	11 (20)	83 (15)	9	76	0	1	1	4
Insomnia	–	73 (13)	–	0	–	2	–	8
Limb pain	–	66 (12)	–	0	–	1	–	5
Lower limb edema	–	62 (11)	–	0	–	3	–	9
Nasal congestion	6 (11)	–	1	–	2	–	2	–
Nausea	30 (54)	179 (33)	12	72	12	58	4	27
Pallor	9 (16)	–	3	–	4	–	2	–
Rhinorrhea	11 (20)	–	0	–	6	–	4	–
Sedation	11 (20)	–	1	–	9	–	1	–
Somnolence	19 (34)	113 (21)	4	33	5	26	9	28
Sweating increased	14 (25)	–	5	–	6	–	3	–
Urinary tract infection	–	77 (14)	–	0	–	0	–	0
Vomiting	12 (21)	66 (12)	6	25	4	19	1	7
Weakness	7 (13)	–	0	–	1	–	2	–
Yawning	24 (43)	86 (16)	6	51	16	27	2	8
Other Notable Harms	–	–	–	–	–	–	–	–
Syncope, postural hypotension, or any hypotension	11 (20)	13 (2)	3	0	2	2	3	3
Syncope	3 (5)	–	0	–	1	–	0	–
Postural hypotension	5 (9)	–	1	–	1	–	2	–
Hypotension	3 (5)	–	2	–	0	–	1	–
Baseline orthostatic hypotension	–	63 (19)	–	–	–	1	–	26

AE =adverse event; APO = apomorphine hydrochloride; CSR = Clinical Study Report; SAE = serious adverse event.

Source: APO 303,[30] APO 303 CSR,[48] APO 401,[10] APO 401 CSR.[15]

Limitations

Although steps were taken to blind patients and clinicians to treatment in the crossover phase in APO 303, a single dose of apomorphine had the potential to reverse symptoms, and patients and clinicians may have deduced the treatment received during one or both visits. The extent to which this would affect the results depends on how objective the outcome measures were. The primary efficacy end points were clinician-evaluated measures such as UPDRS and dyskinesia assessment. The safety end points were objectively measured using electrocardiogram data, clinical laboratory testing, and orthostatic blood pressure monitoring before and after apomorphine dosing. Classification of relatedness of AEs to treatment was done by site investigators, and there was potential for overestimating drug-related AEs.

In the APO 401 trial, only 41% of patients continued trimethobenzamide use throughout the trial. It is not clear why most patients stopped its use, and it is possible that some AEs, particularly nausea and vomiting, could potentially have been reduced with continued trimethobenzamide use. A large number of patients withdrew from the study (424 out of 546), most commonly citing AEs as the reason for withdrawal (34.3%). This large number of discontinuations may bias the results, potentially overestimating or underestimating the frequency of AEs associated with apomorphine, as those remaining in the study may have been better able to tolerate apomorphine. It was also noted that patients did not necessarily treat all “off” episodes with apomorphine, though reasons were not given; therefore, some AEs may have occurred due to lack of apomorphine treatment rather than because of apomorphine treatment.

In the APO 303 trial, a 5% level of significance was chosen for the efficacy analyses for the crossover phase while all other analyses used a 10% significance level; however, the rationale for the 10% significance level was not described. While there was only one primary efficacy end point, several secondary efficacy end points from the crossover phase were tested at a 0.05 significance level without adjustment for multiple comparisons. The last observation carried forward was used to impute missing values for the primary efficacy end point unless all timed observations including pre-dose data were missing. Any imputed values would have been carried forward from the pre-dose or 0-minute post-dose time points and would likely lead to the underestimation of any effect. Information was not available on the numbers of missing values in each group, and it is unclear whether the two groups were affected differently.

Both the APO 303 and APO 401 trials were conducted primarily in patients with advanced PD (H&Y stages 2 to 4 and UPDRS total score of around 55) experiencing “off” episodes refractory to optimized anti-PD medications, and the findings may not be applicable in early-stage PD patients. The APO 401 trial required that the patients be free of clinically significant illnesses and able to self-recognize “off” episodes and maintain daily PD diaries. Therefore, patients with severe comorbidities were likely excluded from this trial. The majority of the patients were white, which may further limit the generalizability of the result if race is an important prognostic factor. Information was not provided for how patients in both studies were recruited, and it is unclear if the study sample was representative of the target population. Also missing is information on how decisions to waive inclusion criteria in APO 401 were made.

Conclusions

In APO 303 and APO 401, long-term safety data were presented for PD patients who were mostly classified as stages 2 to 4 on the H&Y scale with a mean UPDRS total score of around 55. While 187 out of 546 patients in the main study withdrew due to AEs, most patients extended their apomorphine therapy duration past one year. Common AEs were known effects of apomorphine and included nausea, vomiting, dyskinesia, dizziness, somnolence, and injection site bruising. Of the SAEs recorded, 27 SAEs in 19 patients may have been related to apomorphine treatment, with the most common events being syncope, drug-induced psychosis, postural hypotension, and fall. Incidence of orthostatic hypotension increased following apomorphine injection, though this change was not different compared with placebo injection in the smaller substudy. The substudy demonstrated that a 4 mg dose of apomorphine was effective in reducing motor dysfunction as measured by the UPDRS motor score before and 20 minutes after injection.

Appendix 7: Summary of the Systematic Review by Deleu et al.

Aim

The aim of this appendix is to summarize and critically appraise the systematic review by Deleu et al.,[49] since results reported in this review for the outcome of time spent in an "off" state were used to help inform the pharmacoeconomic review. This systematic review provided a comprehensive overview on the therapeutic and safety profile of intermittent or continuous subcutaneous injection or infusion of apomorphine in Parkinson's disease (PD). Although the Deleu et al. review discussed pharmacokinetics, dynamics, indications to determine dopaminergic responsiveness, and drug interactions, this current report will be limited to the clinical evidence for the efficacy and safety of intermittent subcutaneous injection of apomorphine.

Methods

All available relevant literature from January 1960 to May 2004 was searched in the MEDLINE, EMBASE, Current Contents, and AdisBase database using the following keywords: "Parkinson's disease," "apomorphine," and "subcutaneous." In addition, references from pertinent articles were searched and standard textbooks on neurology, pharmacology, and PD were consulted for relevant evidence. Clinical trials, non-randomized studies, observational studies, non-comparative studies, and abstracts were reviewed. The primary outcomes measured in most clinical trials were reduction in time spent in "off" state and improvement in UPDRS-III motor score following apomorphine treatment. Exclusion criteria included insufficient data on the duration of "off" episodes before and after apomorphine treatment, sample size consisting of fewer than 10 patients, follow-up period of less than one month, studies with non-subcutaneous route of administration, duplicate reports with the same set of patients, and non-idiopathic forms of PD.

Critical Appraisal

The systematic review was conducted to provide a comprehensive evaluation of the use of subcutaneous apomorphine in its different indications for PD. Other than the overall aim of evaluating subcutaneous apomorphine treatment, clear research questions and inclusion criteria were not provided. Even though the literature search strategy was comprehensive, there is no information on whether study selection and data extraction were done by two or more reviewers. While references were provided for the included studies, a list was not provided for the excluded studies. The authors of the systematic review declared no conflicts of interest, but did not provide this information for the included studies. The included studies were each assigned one of five classes of evidence, though these classes were mainly based on study design as opposed to a formal quality assessment.

With the exception of the APO 202 study,[16] all of the included studies were small, open-label, uncontrolled studies with sample sizes ranging from 11 to 49. The only baseline characteristics provided for all of the studies were age and duration of disease. From the few values of Hoehn and Yahr stage and duration of levodopa treatment provided, it is apparent that the disease characteristics varied between studies. Other than identifying the study designs of the included studies, there is no mention of any assessment of their scientific quality or heterogeneity. The individual study data were not aggregated using standard

techniques for pooling data in meta-analysis. Instead, the means (or median for one study) of patient characteristics and outcome measures reported in the individual studies were pooled as unweighted means. Likelihood of publication bias was not assessed.

It is difficult to compare the studies owing to the differences in study design, baseline characteristics, apomorphine dosage, follow-up duration, and outcomes measured. Given these apparent differences and the absence of an assessment of heterogeneity, a narrative summary of the results would have sufficed. While all studies that used intermittent subcutaneous apomorphine injection measured changes in time spent in “off” phase, changes in dyskinesia intensity and daily duration were not reported in several studies. Change in UPDRS-III motor score with apomorphine dosing is an important measure to determine efficacy of treatment and is commonly used in clinical trials, but was reported in only three of the included studies.

Results

Efficacy of Intermittent Subcutaneous Apomorphine

The majority of clinical trials were designed to investigate the efficacy of subcutaneous apomorphine (either intermittent injection or continuous infusion) in reversing acute, unexpected, and refractory “off” episodes among patients with late-stage PD on levodopa. Overall, only one short-term, randomized, double-blind, placebo-controlled trial[16] and one short-term and six long-term open-label uncontrolled trials provided information on the efficacy and safety of intermittent subcutaneous apomorphine injection as an add-on therapy to levodopa. The total number of patients was 195. The one controlled trial was from the publication based on study APO 202.

Table 33 and Table 34 show the individual study values and unweighted pooled means for patient characteristics, intervention parameters, and outcome measures. Out of the eight studies, six found a significant reduction in daily time in “off” state compared with either placebo or pre-apomorphine values. The one controlled study had the lowest reduction in “off” time out of all the studies. Two of the five studies reporting daily time spent “on” with dyskinesia found a reduction with apomorphine treatment. Besides the controlled study, two studies reported a mean reduction of 32% in UPDRS motor score.

Table 33: Patient Characteristics From Primary Studies Using Intermittent Subcutaneous Apomorphine

	n	Mean Age, Years (Range or SD)	Mean Duration of PD, Years (Range or SD)	Mean Hoehn and Yahr Stage (Range)	Mean Duration of Levodopa Treatment, Years (Range)
	29	66 (2)	9.2 (1.1)	NR	NR
	32	59 (40 to 73)	14.5 (5 to 23)	3.5 (2 to 5)	12.9 (3 to 20)
	11	57.6 (42 to 67)	13.5 (10 to 19)	3.8 (3 to 4)	12 (9 to 19)
	24	58.9 (9.7)	11.5* (3 to 25)	4[a]	NR
	49	62.6 (42 to 78)	15.2 (5 to 26)	NR	NR
	12	57.4 (44 to 68)	10.8 (2.5 to 18)	3.6 (3 to 4)	NR
	22	59.3 (44 to 76)	9.8 (3.4 to 19.2)	(2 to 4)	8 (3 to 19)
	16	59.7 (48 to 79)	13.9 (9 to 28)	3.8 (2 to 5)	NR
Unweighted Pooled Mean	Total N = 195	60.0	12.3	3.6	10.9

NR = not reported; PD = Parkinson's disease; SD = standard deviation.

[a] Median.

Source: From Drugs & Aging, Deleu D, Hanssens Y, and Northway MG, Subcutaneous Apomorphine: An Evidence-Based Review of its Use in Parkinson's Disease, 2004, Volume 21(11), Pages 687–709, Copyright © 2004 Adis Data Information BV, with permission from Springer. CADTH does not own this work and permission should be sought from the copyright owner. Table IV. Summary of the main findings of studies using intermittent subcutaneous apomorphine injections in the long-term treatment of advanced Parkinson's disease.[49]

Table 34: Apomorphine Intervention and Results From Primary Studies Using Intermittent Subcutaneous Apomorphine

	APO Treatment				Change (Vs. APO Pre-Treatment or PLB)	
Author, Year	Mean Follow-Up Duration, Months (Range)	Mean Dose/ Injection, mg (Range)	Mean Number of Doses (Range or SD)	Mean Total Dose/Day, mg (Range)	Mean Daily Time in "Off" State, %	Mean Daily Time in "On" State With Dyskinesia, %
Dewey et al. (2001)[16]	1	5.4	2.5 (0.2)	NR	−33, $P \leq 0.02$[a]	24[a]
Frankel et al. (1990)[34]	13.5 (5 to 26)	2.2 (0.2 to 5.0)	4.8 (2 to 18)	10.2 (0.8 to 27.5)	−58, $P < 0.02$	NR
Esteban et al. (1997)[50]	23 (4 to 40)	3 (2 to 4)	3 (1 to 5)	9	−45, $P < 0.01$	NR
Pietz et al. (1998)[33]	22[b] (6 to 54)	1.9[b] (0.5 to 4.5)	5.1[b] (2 to 13)	9.7[b] (2 to 26)	−41, P 0.001	8
Hughes et al. (1993)[32]	27 (12 to 54)	(2 to 5)	(2 to 7)	18.6 (0.4 to 75)	−42	NR
Poewe et al. (1989)[51]	6.5	4 (2.5 to 7)	2 (1 to 5)	9.6 (5 to 15)	−56	NR
Ostergaard et al. (1995)[29]	2	3.4 (0.8 to 6.0)	NR	NR	−43, $P < 0.002$	67
Merello and Leiguarda (1995)[52]	12	3.7 (2 to 6)	4.3 (1 to 8)	17.9 (4 to 36)	−53, $P < 0.03$	NR
Unweighted pooled mean	13.4	3.4	3.6	12.5	−46, P 0.0002	33

APO = apomorphine; NR = not reported; PLB = placebo; SD = standard deviation; vs. = versus.

[a] Versus placebo.

[b] Median.

Source: From Drugs & Aging, Deleu D, Hanssens Y, and Northway MG, Subcutaneous Apomorphine: An Evidence-Based Review of its Use in Parkinson's Disease, 2004, Volume 21(11), Pages 687–709, Copyright © 2004 Adis Data Information BV, with permission from Springer. CADTH does not own this work and permission should be sought from the copyright owner. Table IV. Summary of the main findings of studies using intermittent subcutaneous apomorphine injections in the long-term treatment of advanced Parkinson's disease.[49]

Adverse Events Associated With Intermittent Subcutaneous Apomorphine

The review summarized the adverse events (AEs) and reasons for dropout reported by the individual studies, most of which were related to subcutaneous drug administration and dopaminergic stimulation. The frequencies of different AEs associated with intermittent subcutaneous apomorphine injection are given in Table 35. Percentages were given for each type of AE though it is not clear how these values were defined. It is also unclear why lack of efficacy was reported separately for patients receiving apomorphine and placebo in Study 202 and the other AEs in the same study were not summarized in this manner. The most frequent local AE was subcutaneous fibrotic nodules at the administration site. The most frequent systemic AEs were nausea/vomiting, orthostatic hypotension, and rhinorrhea/lacrimation. Of the patients who withdrew due to an AE, the most frequent reasons were lack of efficacy, hypotension/orthostatic hypotension, and nausea/vomiting. The most frequent neuropsychiatric AE was sedation/drowsiness.

Table 35: Adverse Events Associated With Intermittent Subcutaneous Apomorphine

AEs and Reasons for Dropout	Number of Events
Local AEs	
SC fibrotic nodules	20
Scarring with ulceration	2
Neuropsychiatric AEs	
Confusion	2
Hallucinations/delusions	3
Hypersexuality	1
Insomnia	2
Decrease in libido	1
Sedation/drowsiness	11
Systemic AEs	
Chest pain	3
Diarrhea	1
Edema	2
Flushing	2
Headache	2
Nausea/vomiting	32
Orthostatic hypotension	10
Rhinorrhea/lacrimation	10
Vertigo	2
Yawning	14
Reasons for dropouts	
Chest pain	1
Death	1
Dyskinesia	2
Hypotension/orthostatic hypotension	4
Lack of efficacy	5 1[a]
Lost to follow-up	1
Nausea/vomiting	4
Neuropsychiatric	2
Protocol violation	2
Technical difficulties	3

AE = adverse event.

[a] Patients receiving placebo.

Source: From Drugs & Aging, Deleu D, Hanssens Y, and Northway MG, Subcutaneous Apomorphine: An Evidence-Based Review of its Use in Parkinson's Disease, 2004, Volume 21(11), Pages 687–709, Copyright © 2004 Adis Data Information BV, with permission from Springer. CADTH does not own this work and permission should be sought from the copyright owner. Table VI. Adverse drug reaction profile and reasons for dropout in the clinical trials with intermittent subcutaneous (SC) injections and continuous subcutaneous infusions of apomorphine.[49]

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Conclusions

The systematic review summarized in this appendix identified eight studies that measured efficacy of intermittent subcutaneous apomorphine in reducing time spent in the “off” state in PD patients on levodopa. All of the studies were small (fewer than 50 patients) and only one (APO 202) was randomized and placebo-controlled. There were a number of issues with the systematic review, including a lack of quality assessment of the primary studies and a lack of heterogeneity among the studies that does not support the use of a meta-analysis. Six of the primary studies found a significant reduction in daily time in “off” state compared with either placebo or pre-apomorphine values with reductions ranging from 33% to 58%. The most frequent AEs reported across the studies were subcutaneous fibrotic nodules at the administration site, nausea/vomiting, orthostatic hypotension, and rhinorrhea/lacrimation. The most frequent AEs leading to withdrawal from studies were lack of efficacy, hypotension/orthostatic hypotension, and nausea/vomiting. In conclusion, given the limitations of the systematic review and the lack of clarity on pooled daily time in “off” state, there is substantial uncertainty in using the results as an input into the economic model.

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References

1. Clinical Study Report: APO202. A prospective, randomized, double-blind, placebo-controlled parallel groups study of the safety and efficacy of subcutaneous injections of apomorphine in the treatment of "off' episodes in patients with "on-off' or "wearing-off' effects associated with late stage Parkinson's disease [CONFIDENTIAL internal manufacturer's report]. Durham (NC): Bertek Pharmaceuticals Inc.;
2. Clinical Study Report: APO301. A prospective, randomized, placebo-controlled crossover study of the aafety and effectiveness of subcutaneous injections of apomorphine in the treatment of "off" episodes in patients with "on/off" or "wearing-off" effects associated with late stage Parkinson 's Disease. [CONFIDENTIAL internal manufacturer's report]. Durham (NC): Bertek Pharmaceuticals Inc.; 2000 Mar 15; amended 2002 Aug.
3. Clinical Study Report: APO302. A prospective, randomized, placebo-controlled parallel groups study of the continued efficacy and safety of subcutaneous injections of apomorphine in the treatment of off episodes in patients with "on/off" or "wearing-off" effects associated with late-stage Parkinson's Disease after apomorphine use for at least a three month duration [CONFIDENTIAL internal manufacturer's report]. Durham (NC): Bertek Pharmaceuticals Inc.; 2002 Nov.
4. Health Canada reviewer's report: Movapo (Apomorphine hydrochloride injection) [CONFIDENTIAL internal report]. Ottawa: Therapeutics Products Directorate, Health Canada; 2016 Nov 21.
5. Wong SL, Gilmour H, Ramage-Morin PL. Parkinson's disease: prevalence, diagnosis and impact [Internet]. Ottawa: Statistics Canada; 2014. [cited 2017 Aug 9]. (Health reports; catalogue no. 82-003-X). Available from: http://www.statcan.gc.ca/pub/82-003-x/2014011/article/14112-eng.pdf
6. Jankovic J. Etiology and pathogenesis of Parkinson disease. In: Post TW, editor. UpToDate [Internet]. Waltham (MA): UpToDate; 2017 Jul 17 [cited 2017 Aug 3]. Available from: www.uptodate.com Subscription required.
7. Canadian guidelines on Parkinson's disease. Can J Neurol Sci [Internet]. 2012 Jul [cited 2017 Aug 2];39(4):Suppl 4. Available from: www.parkinsonclinicalguidelines.ca/sites/default/files/PD_Guidelines_2012.pdf
8. Tarsy D. Pharmacologic treatment of Parkinson disease. In: Post TW, editor. UpToDate [Internet]. Waltham (MA): UpToDate; 2017 Mar 29 [cited 2017 Aug 3]. Available from: www.uptodate.com Subscription required.
9. PrMovapo™ (apomorphine hydrochloride): pre-filled pens and ampoules: 10 mg/ml [product monograph]. St-Laurent: Paladin Labs Inc; 2016 Nov 21.
10. LeWitt PA, Ondo WG, Van Lunen B, Bottini PB. Open-label study assessment of safety and adverse effects of subcutaneous apomorphine injections in treating "off" episodes in advanced Parkinson disease. Clin Neuropharmacol. 2009 Mar;32(2):89-93.
11. PrNeupro® (rotigotine): 1 mg/24h, 2 mg/24h, 3 mg/24h, 4 mg/24h, 6 mg/24h, 8 mg/24h [product monograph] [Internet]. Oakville (ON): UCB Canada Inc.; 2017 Aug 8. [cited 2017 Oct 3]. Available from: https://pdf.hres.ca/dpd_pm/00040663.PDF
12. PrRequip® (ropinirole hydrochloride tablets): 0.25 mg, 1.0 mg, 2.0 mg, 5.0 mg ropinirole [product monograph] [Internet]. Mississauga (ON): GlaxoSmithKline Inc.; 2017 Apr 4. [cited 2017 Oct 3]. Available from: https://pdf.hres.ca/dpd_pm/00038793.PDF
13. PrMirapex® (pramipexole dihydrochloride tablets): 0.125 mg, 0.25 mg, 0.5 mg, 1.0 mg, 1.5 mg [product monograph] [Internet]. Burlington (ON): Boehringer Ingelheim (Canada) Ltd.; 2017 Jul 25. [cited 2017 Oct 3]. Available from: https://pdf.hres.ca/dpd_pm/00040390.PDF
14. CDR submission: Movapo™ (apomorphine hydrochloride) injection, supplied as pre-filled pens and ampoules, 10mg/mL, 3 mL. Company: Paladin Labs Inc. [CONFIDENTIAL manufacturer's submission]. St-Laurent (QC): Paladin Labs Inc.; 2017 Jun.
15. Clinical Study Report: APO401. A open label study to evaluate the long-term safety and effectiveness of subcutaneous injections of apomorphine in the treatment of "off" episodes in patients with "on-off" or "wearing-off" effects associated with late-stage Parkinson's Disease [CONFIDENTIAL internal manufacturer's report]. Canonsburg (PA): Mylan Pharmaceuticals, Inc.; 2002 Aug 19.
16. 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 Sep;58(9):1385-92.
17. Pfeiffer RF, Gutmann L, Hull KL, Jr., Bottini PB, Sherry JH, APO302 Study Investigators. Continued efficacy and safety of subcutaneous apomorphine in patients with advanced Parkinson's disease. Parkinsonism Relat Disord. 2007 Mar;13(2):93-100.
18. Shulman LM, Gruber-Baldini AL, Anderson KE, Fishman PS, Reich SG, Weiner WJ. The clinically important difference on the unified Parkinson's disease rating scale. Arch Neurol. 2010 Jan;67(1):64-70.
19. Forjaz MJ, Martinez-Martin P. Metric attributes of the unified Parkinson's disease rating scale 3.0 battery: part II, construct and content validity. Mov Disord. 2006 Nov;21(11):1892-8.
20. Schrag A, Sampaio C, Counsell N, Poewe W. Minimal clinically important change on the unified Parkinson's disease rating scale. Mov Disord. 2006 Aug;21(8):1200-7.
21. Martinez-Martin P, Forjaz MJ. Metric attributes of the unified Parkinson's disease rating scale 3.0 battery: Part I, feasibility, scaling assumptions, reliability, and precision. Mov Disord. 2006 Aug;21(8):1182-8.
22. Metman LV, Myre B, Verwey N, Hassin-Baer S, Arzbaecher J, Sierens D, et al. Test-retest reliability of UPDRS-III, dyskinesia scales, and timed motor tests in patients with advanced Parkinson's disease: an argument against multiple baseline assessments. Mov Disord. 2004 Sep;19(9):1079-84.

23. Martignoni E, Franchignoni F, Pasetti C, Ferriero G, Picco D. Psychometric properties of the Unified Parkinson's Disease Rating Scale and of the Short Parkinson's Evaluation Scale. Neurol Sci. 2003 Oct;24(3):190-1.

24. Siderowf A, McDermott M, Kieburtz K, Blindauer K, Plumb S, Shoulson I, et al. Test-retest reliability of the unified Parkinson's disease rating scale in patients with early Parkinson's disease: results from a multicenter clinical trial. Mov Disord. 2002 Jul;17(4):758-63.

25. Richards M, Marder K, Cote L, Mayeux R. Interrater reliability of the Unified Parkinson's Disease Rating Scale motor examination. Mov Disord. 1994 Jan;9(1):89-91.

26. Hauser RA, Gordon MF, Mizuno Y, Poewe W, Barone P, Schapira AH, et al. Minimal clinically important difference in Parkinson's disease as assessed in pivotal trials of pramipexole extended release. Parkinsons Dis [Internet]. 2014 [cited 2017 Sep 19];2014:467131. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3995302

27. Statistical principles for clinical trials. ICH harmonised tripartite guideline [Internet]. London: European Medicines Agency; 1998 Sep. [cited 2017 Oct 20]. (ICH topic E9). Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002928.pdf

28. Webster DD. Critical analysis of the disability in Parkinson's disease. Mod Treat. 1968 Mar;5(2):257-82.

29. Ostergaard L, Werdelin L, Odin P, Lindvall O, Dupont E, Christensen PB, et al. Pen injected apomorphine against off phenomena in late Parkinson's disease: a double blind, placebo controlled study. J Neurol Neurosurg Psychiatry [Internet]. 1995 Jun [cited 2017 Aug 11];58(6):681-7. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1073544

30. 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 Jul 15;258(1-2):137-43.

31. Trosch RM, Silver D, Bottini PB. Intermittent subcutaneous apomorphine therapy for 'off' episodes in Parkinson's disease: a 6-month open-label study. CNS Drugs. 2008;22(6):519-27.

32. Hughes AJ, Bishop S, Kleedorfer B, Turjanski N, Fernandez W, Lees AJ, et al. Subcutaneous apomorphine in Parkinson's disease: response to chronic administration for up to five years. Mov Disord. 1993 Apr;8(2):165-70.

33. Pietz K, Hagell P, Odin P. Subcutaneous apomorphine in late stage Parkinson's disease: a long term follow up. J Neurol Neurosurg Psychiatry [Internet]. 1998 Nov [cited 2017 Aug 11];65(5):709-16. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2170363

34. Frankel JP, Lees AJ, Kempster PA, Stern GM. Subcutaneous apomorphine in the treatment of Parkinson's disease. J Neurol Neurosurg Psychiatry [Internet]. 1990 Feb [cited 2017 Aug 8];53(2):96-101. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC487943

35. Van Laar T, Jansen EN, Essink AW, Neef C, Oosterloo S, Roos RA. A double-blind study of the efficacy of apomorphine and its assessment in 'off'-periods in Parkinson's disease. Clin Neurol Neurosurg. 1993 Sep;95(3):231-5.

36. Nomoto M, Kubo S, Nagai M, Yamada T, Tamaoka A, Tsuboi Y, et al. A Randomized Controlled Trial of Subcutaneous Apomorphine for Parkinson Disease: A Repeat Dose and Pharmacokinetic Study. Clin Neuropharmacol. 2015 Nov;38(6):241-7.

37. Hattori N, Nomoto M, Study Group. Sustained efficacy of apomorphine in Japanese patients with advanced Parkinson's disease. Parkinsonism Relat Disord. 2014 Aug;20(8):819-23.

38. Isaacson S, Lew M, Ondo W, Hubble J, Clinch T, Pagan F. Apomorphine Subcutaneous Injection for the Management of Morning Akinesia in Parkinson's Disease. Mov disord clin pract [Internet]. 2017 Jan [cited 2017 Aug 11];4(1):78-83. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5298032/pdf/MDC3-4-78.pdf

39. Kompoliti K, Wang QE, Goetz CG, Leurgans S, Raman R. Effects of central dopaminergic stimulation by apomorphine on speech in Parkinson's disease. Neurology. 2000 Jan 25;54(2):458-62.

40. Hauser RA, Friedlander J, Zesiewicz TA, Adler CH, Seeberger LC, O'Brien CF, et al. A home diary to assess functional status in patients with Parkinson's disease with motor fluctuations and dyskinesia. Clin Neuropharmacol. 2000 Mar;23(2):75-81.

41. Hauser RA, Auinger P, Parkinson Study Group. Determination of minimal clinically important change in early and advanced Parkinson's disease. Mov Disord. 2011 Apr;26(5):813-8.

42. Hauser RA, Deckers F, Lehert P. Parkinson's disease home diary: further validation and implications for clinical trials. Mov Disord. 2004 Dec;19(12):1409-13.

43. Goetz CG, Stebbins GT, Shale HM, Lang AE, Chernik DA, Chmura TA, et al. Utility of an objective dyskinesia rating scale for Parkinson's disease: inter- and intrarater reliability assessment. Mov Disord. 1994 Jul;9(4):390-4.

44. Dewey RB, Jr., Maraganore DM, Ahlskog JE, Matsumoto JY. Intranasal apomorphine rescue therapy for parkinsonian "off" periods. Clin Neuropharmacol. 1996 Jun;19(3):193-201.

45. Collins LM, Lazic SE, Barker RA. A retrospective analysis of hand tapping as a longitudinal marker of disease progression in Huntington's disease. BMC Neurol [Internet]. 2014 Feb 24 [cited 2017 Sep 19];14:35. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3937529

46. Michell AW, Goodman AO, Silva AH, Lazic SE, Morton AJ, Barker RA. Hand tapping: a simple, reproducible, objective marker of motor dysfunction in Huntington's disease. J Neurol. 2008 Aug;255(8):1145-52.

47. Baas H, Stecker K, Fischer PA. Value and appropriate use of rating scales and apparative measurements in quantification of disability in Parkinson's disease. J Neural Transm Park Dis Dement Sect. 1993;5(1):45-61.

48. Clinical Study Report: APO303. Study of orthostatic changes upon apomorphine dose initiation in late-stage Parkinson's Disease patients. A dose escalation study with a double-blind placebo-controlled efficacy determination at 4 mg [CONFIDENTIAL internal manufacturer's report]. Durham (NC): Bertek Pharmaceuticals Inc.; 2002 Nov.

49. Deleu D, Hanssens Y, Northway MG. Subcutaneous apomorphine : an evidence-based review of its use in Parkinson's disease. Drugs Aging. 2004;21(11):687-709.

50. Esteban MJ, Marti MJ, Marin C, Tolosa E. Long-term treatment with intermitent intranasal or subcutaneous apormorphine in patients with levodopa-related motor fluctuations. Clin Neuropharmacol. 1997 Jun;20(3):245-52.

51. Poewe W, Kleedorfer B, Gersterbrand F, Oertel WH. Die Behandlung von Parkinsonpatienten mit L-Dopa-Wirkungsfluktuation mittels subkutanen Apomorphingaben. Acta Neurolo. 1989;16:73-7.

52. Merello M, Leiguarda R. [Treatment of motor fluctuations in Parkinson's disease with subcutaneous injections of apomorphine]. Medicina (B Aires). 1995;55(1):5-10.