CADTH

CADTH Common Drug Review

Clinical Review Report

Apomorphine hydrochloride (Kynmobi)

(Sunovion Pharmaceuticals Canada Inc.)

Indication: the acute, intermittent treatment of “OFF” episodes in patients with Parkinson disease.

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Abbreviations

ADL	activities of daily living
AE	adverse event
APO SC	apomorphine hydrochloride subcutaneous
APO SL	apomorphine hydrochloride sublingual
CDR	CADTH Common Drug Review
CI	confidence interval
CrI	credible interval
DA	dopamine agonist
EQ VAS	EuroQol Visual Analogue Scale
EQ-5D	EuroQol 5-Dimensions questionnaire
EQ-5D-5L	EuroQol 5-Dimensions 5-Levels questionnaire
ESS	Epworth Sleepiness Scale
HRQoL	health-related quality of life
ITC	indirect treatment comparison
LS	least squares
LTS	long-term safety
MAO-B	monoamine oxidase type B
MCID	minimal clinically important difference
MDS-UPDRS	Movement Disorders Society Unified Parkinson's Disease Rating Scale
mITT	modified intention to treat
MMRM	mixed model repeated measures
MV	maintenance visit
NMA	network meta-analysis
PD	Parkinson disease
PDQ-39	Parkinson's Disease Questionnaire 39
PDQ-8	8-item Parkinson's Disease Questionnaire
PDQSI	Parkinson's Disease Questionnaire Summary Index
PGI-I	Patient Global Impression—Improvement
RCT	randomized controlled trial
SAE	serious adverse event
SD	standard deviation
SE	standard error
SLR	systematic literature review
TEAE	treatment-emergent adverse event
WDAE	withdrawal due to adverse event

Executive Summary

An overview of the submission details for the drug under review is provided in Table 1.

Table 1: Submitted for Review

Item	Description
Drug product	Apomorphine hydrochloride (Kynmobi)
Indication	The acute, intermittent treatment of OFF episodes in patients with Parkinson disease
Reimbursement request	As per indication
Health Canada approval status	NOC
Health Canada review pathway	Standard review
NOC date	June 12, 2020
Sponsor	Sunovion Pharmaceuticals Canada Inc.

NOC = Notice of Compliance.

Introduction

Parkinson disease (PD) is one of the most common neurodegenerative diseases.[1] It is characterized by chronic neurodegeneration of the striatal region of the brain causing a deficiency of dopamine, a neurotransmitter.[2] In North America, it affects between 100 and 200 per 100,000 people older than 40 years of age.[3] Canadian survey data from 2010 to 2012 yielded estimates of prevalence rates for diagnosed PD of 0.2% (55,000 patients) in the household population and 4.9% (12,500 patients) in residents of long-term care facilities.[4] The clinical manifestations of PD include resting tremor, rigidity, bradykinesia, and postural instability leading to loss of control of voluntary movement.[3,5] Besides motor system disorder, PD is also associated with non-motor symptoms, such as cognitive dysfunction and dementia, mood disorders, gastrointestinal symptoms, sleep disturbances, fatigue, pain, and sensory disturbances.[3]

Currently, 4 main drugs have anti-Parkinson activity and are considered symptomatic therapies: levodopa, dopamine agonists (DAs), monoamine oxidase type B (MAO-B) inhibitors, and amantadine.[6] Levodopa remains the most effective oral drug for the management of motor symptoms in the early stages of PD; however, after 4 to 6 years of levodopa therapy, approximately 40% to 50% of patients experience motor fluctuations or dyskinesia.[2,5,7] Motor fluctuations, also called “ON-OFF” fluctuations, are changes in the patient’s ability to move. It is considered a consequence of progressive degeneration of the nigrostriatal dopamine terminals.[8] A patient’s quality of life is severely affected, as motor fluctuations significantly affect their daily life, work, hobbies, and social activities.[9] DAs have a role in patients with advanced PD as a treatment for motor complications of levodopa.[6] Apomorphine hydrochloride is a non-ergot DA. It can be administered through a variety of routes, including subcutaneous, transdermal, nasal or pulmonary, sublingual, and rectal.[10,11] Subcutaneous apomorphine hydrochloride (APO SC) (Movapo) was reviewed by the CADTH Common Drug Review (CDR) in 2017, and it was recommended to be reimbursed as adjunctive therapy in coping with OFF episodes for patients who are receiving optimized PD therapy.[12] Kynmobi is apomorphine hydrochloride sublingual (APO SL) film. It was first submitted to CADTH for a pre–Notice of Compliance (NOC) review in February 2019. The proposed indication was for the acute, intermittent treatment of hypomobility; OFF episodes associated with PD, including end-of-dose wearing OFF (including early-morning OFF); partial, delayed, or no ON episodes; and unpredictable OFF.

[redacted]. Therefore, the sponsor withdrew the application from the CDR process and the CADTH Canadian Drug Expert Committee (CDEC) did not review this drug. In June 2020, the sponsor refiled the submission to CADTH after APO SL received an NOC from Health Canada on June 12, 2020. The approved indication is for acute, intermittent treatment of OFF episodes in patients with PD.[13] The reimbursement criteria for APO SL film requested by the sponsor is the same as the Health Canada–approved indication. In this refiled submission, the sponsor provided a published full report of the pivotal study (not available at the time of the previous submission) and long-term efficacy and safety data for APO SL for up to 48 weeks of treatment.

Dose titration is initiated with a single dose of 10 mg of APO SL film when patients are in an OFF state. When the patient tolerates the dose but does not respond adequately (does not turn ON), the patient should resume their usual PD medication and up-titrate the dose of APO SL at the next observed OFF period, generally within 3 days, and then continue to titrate in a similar manner in 5 mg increments until an effective and tolerable dose is achieved, up to 30 mg. Doses should be separated by at least 2 hours, and the treatment administered should not exceed 5 films per day. The total daily dose should not exceed 90 mg.[14]

The objective of the current CDR review was to perform a systematic review of the beneficial and harmful effects of APO SL film (Kynmobi) for the acute, intermittent treatment of OFF episodes in patients with PD.

Stakeholder Engagement

The information in this section is a summary of input provided by the patient groups that responded to CADTH's call for patient input and received from the clinical expert(s) consulted by CADTH for the purpose of this review.

Patient Input

Five patient groups submitted input for the review of APO SL: the Michael J. Fox Foundation, the Parkinson Association of Alberta, Parkinson Canada, Parkinson Society British Columbia, and Parkinson Québec. They are all non-profit organizations that provide support services and education to people living with PD and their caregivers and families, and health care professionals. These patient groups gathered patient input via surveys, phone interviews, and a guidebook published by the patient group itself.

The patient groups described the experience of living with PD, saying that PD is a heterogeneous condition that encompasses a large number of motor and non-motor symptoms experienced by each patient to different degrees, from mild to severe. Early-stage disease symptoms may affect a patient's ability to work, socialize, exercise, eat, sleep, and perform daily tasks. Mid- and late-stage disease often involves speech impairment, hypophonia, swallowing problems, drooling, poor stomach emptying, flexed or bent posture, postural instability, rigidity in neck and trunk, motor fluctuations, and dyskinesia (which can progress into more severe walking problems), instability, shuffling, festination, and freezing of gait. PD psychosis or dementia can occur. Almost half of respondents felt their family and social relationships were negatively impacted by the disease and a large majority had experienced a loss in quality of life and ability to participate in recreational activities and exercise.

The main and most effective treatment for PD is levodopa; however, levodopa poses a higher risk of long-term side effects and motor complications. The nature of PD treatments leads to 2 states experienced during the day: ON and OFF. The OFF state is associated with a much higher degree of disability and loss of confidence than the ON state. There is an unmet need among people with PD for medications that offer better symptom control with fewer side effects and for add-on therapies that provide a "grace period" during the OFF state. The patient groups responding to this call for input did not have experience with APO SL. Patients who experience OFF episodes are looking for medications that can provide relief during these troublesome or debilitating periods of the day.

Clinician Input

Currently available medical therapies for PD are symptomatic therapies; that is, they treat the symptoms and the disability suffered by the patient. Most expert guidelines and recommendations review treatment in motor and non–motor symptom categories.

Motor symptoms are the movement problems caused by PD, including tremor, bradykinesia, rigidity, gait difficulty, as well as effects on motor functions like chewing, swallowing, and speech. Non-motor symptoms include sleep disorders, cognitive and neuropsychiatric symptoms, autonomic nervous system dysfunction, sensory symptoms, and pain.

Treatment of motor disability (e.g., motor symptoms that prevent completion of daily activities) is usually a key treatment target. As disease progresses, the need for treatment and the manner in which treatment works for motor symptoms evolve: treatment effects become shorter and more unreliable, and patients spend more waking hours with functional impairment, including nighttime and early-morning symptoms.

Most available medical therapies for motor symptoms have a delayed clinical effect, and APO SL (Kynmobi) works quickly. This provides a tool that patients can apply for a short-term effect on motor symptoms, as is needed with sudden, unexpected emergence of symptoms, symptoms that emerge in the night when oral medication scheduling is not practical, and ineffective or partially effective oral medication doses.

In the expert's opinion, patients who frequently (i.e., more than weekly) find themselves suddenly or urgently in need of treatment for motor symptoms despite attempts at optimizing oral medications should or will receive Kynmobi in practice. For instance, patients experience OFF episodes or a sudden need for motor-symptom treatment despite 5 or more oral medication doses per day. These episodes may occur overnight, early in the morning, from an ineffective dose, or as a feature of complex motor fluctuations.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

One phase III, multi-centre, double-blind, placebo-controlled randomized controlled trial (RCT), CTH-300 (N = 109), met the inclusion criteria for this systematic review. The primary objective of CTH-300 was to evaluate the efficacy and safety of APO SL versus placebo in patients with PD over a 12-week period. The trial included adult patients with idiopathic PD, with a clinically meaningful response to levodopa therapy and with at least 1 OFF episode per day. It contained 2 phases. In the open-label dose titration phase, if the patient

responded to a single, escalating dose of APO SL (started at 10 mg and increased in 5 mg increments to a maximum dose of 35 mg) with a full ON response within 45 minutes of drug administration, that particular dose would be used in the next phase, the double-blind maintenance treatment phase. Any patients who reached 35 mg at the last titration visit (the sixth visit) and did not exhibit a full ON response within 45 minutes were terminated from the study. Patients who completed the dose titration phase entered the maintenance treatment phase and were randomly assigned to 12 weeks of treatment with APO SL or placebo. A total of 214 patients were screened. Among them, 141 (65.9%) were enrolled into the dose titration phase. Among the 141 patients who entered the dose titration phase, 109 completed this phase and were randomized to the study drugs: 54 to APO SL therapy and 55 to placebo. The average number of daily doses was 2.2 in the APO SL group and 2.5 in the placebo group. In general, the 2 treatment groups were similar in baseline patient characteristics, except that those in the APO SL group had a shorter disease duration compared with those in the placebo group. During the maintenance phase, 37% of the APO-treated patients and 16% of placebo-treated patients discontinued treatment. This is considered clinically significant. The main reason for withdrawal was adverse events (AEs): 28% in the APO SL group and 9% in the placebo group. The primary efficacy end point was the mean change in the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III score from pre-dose to 30 minutes post dose at the week 12 visit of the maintenance treatment phase. Other efficacy outcomes in CTH-300 included frequency of the patient-rated 30 minutes post dose full ON response, change in PD symptoms (e.g., sleepiness disorder) and health-related quality of life (HRQoL). These outcomes were considered important according to patient input and the consulted clinical expert. The MDS-UPDRS is commonly used in practice to measure the change in mobility in patients with PD. The efficacy analyses were performed in a modified intention-to-treat (mITT) population, which included all patients who were randomized and received at least 1 post-randomization dose of the study drug. The safety profile of APO SL was examined, as well.

A hierarchical testing approach was used for the analyses of the primary and secondary efficacy end points to control for multiplicity. Ten efficacy end points were included in this procedure. Statistical significance was not achieved for the secondary end point ranked third in the hierarchical testing (percentage of patients at week 12 with a patient-rated full ON response within 30 minutes post dose that had a duration of at least 30 minutes); therefore, statistical significance cannot be formally claimed for any of the end points ranked after this end point.

Efficacy Results

In the mITT population, the mean change in the MDS-UPDRS Part III score (primary end point) from pre-dose to 30 minutes post dose for the APO SL group (−11.1 points; standard deviation [SD], 1.46) was significantly lower compared with placebo (−3.5 points; SD, 1.29), and the least squares (LS) mean treatment difference (APO SL minus placebo) was −7.6 points (95% confidence interval [CI], −11.5 to −3.7; P = 0.0002). This was considered to be a clinically significant change according to the clinical expert and considered a minimal clinically important difference (MCID) for MDS-UPDRS Part III. In the MDS-UPDRS, lower scores indicate less disability and better mobility. The results of sensitivity analyses supported the findings from the primary analysis. The results of the pre-specified subgroup analyses of the primary end point, based on age, race, baseline pre-dose MDS-UPDRS Part III score, or dose assigned, were generally consistent with those from the primary analyses. Note there was no adjustment for multiplicity in the subgroup analyses.

Additional outcomes were measured as secondary end points, such as percentage of patients with a full ON response within 30 minutes at week 12, mean change from baseline to week 12 in the Parkinson's Disease Questionnaire 39 (PDQ-39), Patient Global Impression–Improvement (PGI-I), and time to effect. Percentage of patients with a patient-rated full ON response within 30 minutes post dose at week 12 was the key secondary end point in CTH-300. A statistically significant difference was observed in favour of APO SL versus placebo in the percentage of patients achieving a full ON response within 30 minutes after drug administration at week 12 (predicted response rate: 35% for APO SL versus 16% for placebo; adjusted odds ratio, 2.81; 95% CI, 1.04 to 7.64; P = 0.0426). For this outcome, missing data were treated as nonresponse. The percentage of patients with a full post-dose ON response that had a duration of at least 30 minutes at week 12 was 31% in the APO SL group and 14% in the placebo group; however, a statistically significant difference was not detected for this outcome (adjusted odds ratio, 2.80; 95% CI, 1.00 to 7.84; P = 0.0501). The between-group difference in change from baseline in the PDQ-39 summary index (Parkinson's Disease Questionnaire Summary Index [PDQSI]) score at week 12 was not statistically significant (APO SL, 0.31 versus placebo, −1.67; mean difference, 1.98; 95% CI, −2.16 to 6.12; P = 0.34). Patients treated with APO SL (37%) were more likely to report "improved" than those treated with placebo (20%) at week 12 using the PGI-I instrument. The median time to when study medication started to have an effect at week 12 was 21 minutes for APO SL, while it was not estimable in the placebo group.

Change in sleepiness disorders measured with the Epworth Sleepiness Scale (ESS) was numerically similar between APO SL and placebo. The change in the ESS summary score at week 12 was 0.5 and −0.6 for APO SL and placebo, respectively. An MCID for ESS in patients with PD was not identified in the literature. The change in the EuroQol 5-Dimensions (EQ-5D) 5-Levels (EQ-5D-5L) questionnaire health index score was −0.03 and 0 for APO SL and placebo, respectively. Note that change in ESS and EQ-5D-5L were not adjusted for multiplicity.

Results of the efficacy analyses suggest a statistically and clinically significant improvement in motor function measured with the MDS-UPDRS Part III score. In addition, significantly more patients treated with APO SL achieved a full ON response 30 minutes after drug administration compared with placebo. Patients in the APO SL group were more likely to indicate improvement in the disease after treatment compared with the placebo group. Significant changes in HRQoL were not observed at week 12 in CTH-300.

Harms Results

During the dose titration phase in CTH-300, the frequency of treatment-emergent adverse events (TEAEs) was 58.2%. During the double-blind maintenance treatment phase, the frequency of TEAEs was higher (88.9%) in the APO SL group compared with the placebo group (45.5%). The majority of AEs were considered mild to moderate. The most common AEs reported with APO were gastrointestinal disorders (31.9% during the dose titration phase; 53.7% for APO SL versus 10.9% for placebo during the maintenance treatment phase), followed by nervous system disorders (26.2% during the dose titration phase; 31.5% for APO SL versus 7.3% for placebo during the maintenance treatment phase); respiratory, thoracic, and mediastinal disorders (22.2% for APO SL versus 1.8% for placebo during the maintenance phase); general disorders and administration-site conditions (18.5% for APO SL versus 7.3% for placebo during the maintenance treatment phase); and psychiatric disorders (14.8% for APO SL versus 3.6% for placebo during the maintenance treatment phase). Isolated cases of serious adverse events (SAEs) were reported, 1 in the

titration phase, and 3 in the maintenance treatment phase: 2 (3.7%) with APO SL and 1 (1.8%) with placebo. Patients treated with APO SL were more likely to withdraw treatment because of AEs (27.8% for APO SL versus 7.3% for placebo) during the maintenance treatment phase. One patient suffered a cardiac arrest and died while being treated with APO SL 15 mg during the maintenance treatment phase, and the death was considered possibly related to treatment by the investigator.

In terms of harms of particular interest, the occurrence of gastrointestinal disorders, application-site reactions (such as stomatitis, oral ulcers, and oral irritation), allergic or sensitivity response to the formulation, daytime sudden onset of sleep, falls and injuries, and hypotension were higher in APO SL–treated patients compared with placebo.

Table 2: Summary of Key Results from CTH-300

Outcome measures	APO SL (N = 54)	Placebo (N = 55)
Efficacy (mITT population)		
Change from pre-dose to 30 minutes post dose in MDS-UPDRS Part III score at week 12[a]		
Pre-dose, mean (SD)	37.2 (12.16)	42.2 (14.88)
Change from pre-dose to 30 minutes post dose, LS mean (SE)	−11.1 (1.46) n = 34	−3.5 (1.29) n = 46
LS mean difference (APO SL minus placebo) (95% CI), P value	−7.6 (−11.5 to −3.7) P = 0.0002	–
Percentage of patients with a full ON response within 30 minutes post dose at week 12[b]		
Yes, n (%)	14 (25.9)	9 (16.4)
No or missing, n (%)	40 (74.0)	46 (83.6)
Predicted response	35%	16%
Adjusted OR (95% CI)	2.81 (1.04 to 7.64) P = 0.0426	–
Percentage of patients with a full ON response within 30 minutes post dose that had a duration of ≥ 30 minutes at week 12		
Yes	22.2%	14.5%
No	40.7%	69.1%
Missing	37.0%	16.4%
Predicted response rate	31%	14%
Adjusted OR (95% CI), P value	2.80 (1.00 to 7.84) P = 0.0501	–
Change from baseline in ESS summary score at week 12		
Baseline, mean (SD)	8.9 (4.16)	9.7 (5.08)
Change from baseline at week 12, mean (SD)	0.5 (3.22) n = 34	−0.6 (3.90) n = 45
Mean difference (APO SL minus placebo) (95% CI), P value	Not reported	–
Change from baseline in PDQ-39 summary index at week 12[c]		
Baseline, mean (SD)	24.34 (13.57)	28.30 (16.21)
Change from baseline at week 12, mean (SD)	0.31 (1.54) n = 32	−1.67 (1.39) n = 45
LS mean difference (APO SL minus placebo) (95% CI), P value	1.98 (−2.16 to 6.12) P = 0.3447	–
PGI-I at week 12, n (%)		

Outcome measures	APO SL (N = 54)	Placebo (N = 55)
Improved[d]	20 (37.0)	11 (20.0)
Not improved[d]	34 (63.0)	44 (80.0)
Time to effect, minutes, median (95% CI)		
	21.2 (15.0 to 27.0)	Not estimable
Safety (maintenance phase safety population)		
Patients with ≥ 1 AE, n (%)	48 (88.9)	25 (45.5)
Patients with ≥ 1 SAE, n (%)	2 (3.7)	1 (1.8)
Patients with ≥ 1 WDAE, n (%)	15 (27.8)	4 (7.3)
Death, n (%)	1 (1.9)	0
Notable harms, n (%)		
Gastrointestinal disorders	[redacted]	[redacted]
Stomatitis, oral ulcers, oral irritation	17 (31.5)	4 (7.3)
Allergic or sensitivity response to the formulation	10 (18.5)	0
Daytime sudden onset of sleep	9 (16.7)	1 (1.8)
Falls and injuries	5 (9.3)	3 (5.5)
Hypotension, orthostatic hypotension	5 (9.3)	0

AE = adverse event; APO = apomorphine hydrochloride; CI = confidence interval; ESS = Epworth Sleepiness Scale; LS = least squares; MDS-UPDRS = Movement Disorders Society Unified Parkinson's Disease Rating Scale; mITT = modified intention to treat; MV = maintenance visit; OR = odds ratio; PDQ-39 = Parkinson's Disease Questionnaire 39; PGI-I = Patient Global Impression—Improvement; SAE = serious adverse event; SD = standard deviation; SE = standard error; SL = sublingual; WDAE = withdrawal due to adverse event.

[a] This was the primary end point. It was analyzed using a mixed model repeated measures (MMRM) analysis, which included the treatment group (APO SL or placebo), visit (MV1, MV2, MV3, and MV4) and the interaction between the treatment group and visit as fixed factors. The change from pre-dose MDS-UPDRS Part III score after 30 minutes, at the last titration visit at which the randomized dose was given up through titration visit 6, was used as a covariate in the model.

[b] This outcome was analyzed in the mITT population based on logistic regression using a generalized linear mixed model procedure. This analysis used the observed values from MV1, MV2, MV3, and MV4 without any imputation as the response. The model included the treatment group and visit and the interaction between the treatment group and visit as fixed factors. The assessment of ON or OFF status at the last titration visit was used as a covariate. In the case of missing data, the patient was considered to have not reached full ON.

[c] Statistics were from an MMRM that included the observed PDQ-39 change from baseline values at MV1, MV2, MV3, and MV4 as the response values. The model included treatment group, visit (MV1, MV2, MV3, and MV4) and the interaction between the treatment group and visit as fixed factors, and the PDQ-39 score from the screening visit as a covariate.

[d] "Improved" included a PGI-I of "very much improved," "much improved" or "minimally improved." "Not improved" included a PGI-I of "no change," "minimally worse," "much worse," or "very much worse."

Source: CTH-300 Clinical Study Report.[15]

Critical Appraisal

A major limitation of CTH-300 was the substantial amount of missing data in the trial, particularly in the APO SL arm. Therefore, there is a high degree of uncertainty with respect to the study findings, which could be biased. Sensitivity analyses were conducted to evaluate the impact of the missing data on study findings. The results of the sensitivity analyses for the handling of missing data supported the findings from the primary analysis. The scales and measures used in CTH-300 were appropriate, according to the clinical expert consulted for this review. Some clinical outcomes that are important to patients were not measured in this study, such as the change in cognition and mood.

Indirect Comparisons

Description of Studies

In the absence of head-to-head trial data on apomorphine versus other active treatments for the management of OFF episodes, the sponsor conducted an indirect treatment comparison (ITC) analysis based on a systematic review of RCTs and compared the clinical efficacy and safety of APO SL (Kynmobi) with APO SC (Movapo). The primary inclusion criteria for the studies included in the search was adult (≥ 18 years) patients with PD who experience intermittent OFF episodes. The primary comparators for the systematic literature review (SLR) and subsequent ITC were sublingual and subcutaneous administrations of apomorphine. A placebo intervention was the only other comparator allowed for a study to be included in the SLR. Conclusions of clinical efficacy were based primarily on mean differences for measures of hypomobility in patients with PD, including MDS-UPDRS and UPDRS motor scores.

Efficacy Results

For the primary outcome of differences in UPDRS or MDS-UPDRS motor score at 20 or 30 minutes, the analysis showed a larger decrease in mean motor score for patients on APO SC compared with those on APO SL, with APO SL patients decreasing 12.40 points less on average (95% credible interval [CrI], 7.63 to 17.17). At 60 minutes from baseline, the results did not favour either treatment (mean difference, −0.52; CrI, −8.01 to 6.98). At 90 minutes from baseline, a statistically significant mean difference was estimated in favour of APO SL (mean difference, −8.21; 95% CrI, −15.02 to −1.38).

Harms Results

The rates of AEs ranged from 32.5% to 88.9% for patients treated with APO SL, and from 70% to 85% for patients treated with APO SC. The authors concluded that the safety results could not be formally compared between APO SL and APO SC primarily due to study heterogeneity.

Critical Appraisal

Key limitations of the ITC included a sparse network and study differences in design and patient characteristics. Neither of these comparisons provided compelling evidence from which to draw conclusions in regard to the comparative efficacy and safety of APO SL versus APO SC.

Other Relevant Evidence

Description of Studies

CTH-301 is a multi-centre, phase III, open-label, single-arm study evaluating the long-term safety (LTS) and efficacy of APO SL in patients with PD who responded to levodopa therapy but still experienced OFF episodes. CTH-301 is ongoing and is expected to be completed in July 2022. Patients could be eligible for CTH-301 if they had completed CTH-201, CTH-203, CHT-300, CTH-301, or CTH-302 (rollover patients) and if, in the opinion of the investigator, they would benefit from continued treatment with APO SL, or if they had not previously participated in a study with APO SL (de novo patients) but met the selection criteria for CTH-301.

After screening, eligible patients (de novo and rollover) entered the dose titration phase to determine an effective dose that could be administered in the LTS phase for treating OFF episodes. Following completion of the titration phase, patients entered the LTS phase (up to 21 days after the final titration visit) and received open-label APO SL treatment. The primary end point is safety and tolerability evaluation.

Efficacy Results

During the LTS phase, the mean decrease in MDS-UPDRS Part III score from pre-dose to 30 minutes post dose overall was [redacted] points on day 1, [redacted] points at month 3, and [redacted] points at month 6 in the study population.

Their findings suggested that after 24 weeks of treatment with APO SL, the improvement in function (assessed using the MDS-UPDRS Part III score) that was observed 24 weeks after study commencement was maintained.

Harms Results

Study CTH-301 provided safety data up to week 48. On the data cut-off date (May 10, 2019) during the dose titration plus LTS phase, AEs were reported in 359 patients ([redacted]%) in the overall population: 66 rollover patients ([redacted]%) and 293 de novo patients ([redacted]%). The majority of the AEs were considered mild to moderate in severity. The most common AEs reported by the study participants were gastrointestinal disorders (51.5%) followed by nervous system disorders ([redacted]%); respiratory, thoracic, and mediastinal disorders (20.9%); general disorders and administration-site conditions ([redacted]%); infection and infestations ([redacted]%); injury, poisoning, and procedural complications ([redacted]%); vascular disorders ([redacted]%); musculoskeletal and connective tissue disorders ([redacted]%); and psychiatric disorders ([redacted]%). De novo patients were more likely to experience AEs compared with those who had received previous APO SL therapy. No deaths were reported during the dose titration phase. Three de novo patients died: 1 due to cardiac arrest, 1 due to drowning, and 1 due to sepsis. One rollover patient died of cardio-respiratory arrest and pneumonia. No deaths were considered treatment related, except for the patient who died of sepsis. For this patient, the relationship of their death to study treatment was considered “unlikely.”

The results suggested that for PD patients with or without experience with previous APO SL therapy, the safety profile of APO SL up to week 48 was generally consistent with that observed in Study CTH-300 (providing safety data up to week 12), with no unexpected safety signals. Due to the nature of the single-arm study, the LTS findings should be interpreted with caution.

Critical Appraisal

The main limitation of Study CTH-301 is the lack of a control group. The study is still ongoing; patients may continue to participate in the study until it is terminated by the sponsor or until APO SL becomes commercially available in the patient’s country. Therefore, the duration of the study is unknown. Even though CTH-301 was designed as a long-term study, the available efficacy and safety data were collected by the data cut-off on May 10, 2019. The results on week 24 are not considered sufficient, given that PD is a chronic, progressive condition and the treatment effect of the study drug on a patient’s physical and mental well-being needs to be explored over the long run. In addition, the results of a number of efficacy outcomes were not available at this time point. By data cut-off, there were patients who had received APO SL for more than 24 weeks. Based on the interim report for CTH-301, 64 patients had received APO SL for longer than 12 months, and 32 patients had results from week 48.

Conclusions

One randomized, double-blind, placebo-controlled trial provides evidence on the efficacy and safety of APO SL as an acute, intermittent treatment for OFF episodes in patients with PD. Overall, after 12 weeks of treatment with APO SL, a statistically significant and clinically meaningful improvement in motor function was observed compared with placebo. Improvement in motor function was measured with change in MDS-UPDRS Part III score from pre-dose to 30 minutes post dose. In addition, treatment with APO SL was also associated with more frequent patient-rated full ON response, more patient-indicated improvement in disease, and a shorter time to effect compared with placebo. However, the differences between APO SL and placebo in change in HRQoL or symptom relief were not significant in the study population. Results of an ITC analysis comparing APO SL with APO SC suggest that the former was associated with a smaller improvement in hypomobility between 20 and 30 minutes after drug administration, but a potentially superior effect after 90 minutes compared with the latter. However, results of the comparative effectiveness between sublingual and subcutaneous apomorphine in this analysis should be interpreted with caution, due to its major limitations.

After 12 weeks of treatment, the incidence of AEs was higher in patients treated with APO SL compared with placebo. The most common AEs included gastrointestinal disorders; nervous system disorders; respiratory, thoracic, and mediastinal disorders; psychiatric disorders; and infections. The AEs were mostly mild to moderate in severity. Serious AEs were not frequently reported in CTH-300. Patients treated with APO SL were more likely to withdraw from treatment due to AEs compared with placebo. An ongoing single-arm LTS study confirms the safety profile of APO SL up to week 48.

Introduction

Disease Background

PD is the second most common neurodegenerative disease after Alzheimer disease.[1] It is characterized by chronic neurodegeneration of the striatal region of the brain causing a deficiency of the neurotransmitter dopamine.[2] In North America, it affects between 100 and 200 per 100,000 people older than 40 years of age.[3] Canadian survey data from 2010 to 2012 yielded estimates of prevalence rates for diagnosed PD of 0.2% (55,000 patients) in the household population and 4.9% (12,500 patients) in residents of long-term care facilities.[4] The mean age at diagnosis ranges from 66 to 71 years, and the incidence of disease increases rapidly after 60 years of age.[3,4] Of those with a PD diagnosis in the Canadian survey, 79% and 97% were at least 65 years of age in the household population and in long-term care facilities, respectively.[4]

The clinical manifestations of PD include resting tremor, rigidity, bradykinesia (slowness of movement), and postural instability leading to loss of control of voluntary movement.[3,5] The impairment in motor functions may worsen over time for the majority of the patients, despite effective symptomatic treatment.[5] After 4 to 6 years of levodopa therapy, approximately 40% to 50% of patients experience motor fluctuations or dyskinesia, and this proportion rises to 90% after 9 or more years of treatment.[7] Motor fluctuations, also called ON-OFF fluctuations, are changes in a patient's ability to move. During ON periods, the patient experiences a positive response to the medication while, during OFF periods, the PD symptoms suppressed during the ON state re-emerge. This is considered a consequence of the progressive degeneration of nigrostriatal dopamine terminals.[8] Initially, the OFF episodes may manifest predictably and occur near the end of each medication dose. As PD progresses, however, the treatment effect of the medication begins to wear off more quickly and the OFF episodes may become more sudden or unpredictable. The patient's quality of life is therefore severely affected when their daily life, work, hobbies, and social activities are difficult to maintain.[9] Besides being a motor system disorder, PD is also associated with non-motor symptoms, such as cognitive dysfunction and dementia, mood disorders, gastrointestinal symptoms, sleep disturbances, fatigue, pain, and sensory disturbances.[3]

Standards of Therapy

The therapies for idiopathic PD vary by the severity of the symptoms and the disease, degree of functional disability, level of physical activity and productivity, patient characteristics, patient preferences, and cost.[5,6] Treatments for motor symptoms can be broadly categorized as pharmacologic, non-pharmacologic (e.g., education, exercise, physiotherapy, and nutrition), and surgical therapy, and patients rely more on medications to maintain their ability to function as the disease progresses.[5,6]

A number of dopaminergic anti-PD medications are marketed worldwide, including in Canada. Four main drugs and drug categories have anti-Parkinson activity and are considered symptomatic therapies: levodopa, DAs, MAO-B inhibitors, and amantadine.[6] Levodopa, a precursor of dopamine, remains the most effective oral drug for the management of motor symptoms in the early stages of PD. The *Canadian Guideline for Parkinson Disease* recommends that 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), MAO-B inhibitors (e.g., rasagiline), anticholinergics

(trihexyphenidyl and procyclidine) or in fixed combination with carbidopa and entacapone (a catechol O-methyltransferase [COMT] inhibitor).[5] The most common early side effects associated with levodopa include nausea, somnolence, dizziness, and headache. More serious adverse reactions to levodopa may include confusion, hallucinations, delusions, agitation, psychosis, and orthostatic hypotension, particularly in older patients.[6] Prolonged used of levodopa may be related to dyskinesia, wearing-OFF episodes (end-of-dose deterioration) and ON-OFF phenomenon (a switch between mobility and immobility).[2,5] Medications with different mechanisms of action can be administered as an adjunct to levodopa in an attempt to reduce OFF time.

DAs are thought to stimulate dopamine receptors directly and do not need to be converted in the brain to be active.[5] It is suggested that DAs have a role as a treatment for motor complications of levodopa in patients with advanced PD.[6] In Canada, commonly prescribed DAs include non–ergot-derived DAs such as ropinirole, pramipexole, and rotigotine, as well as ergot-derived DAs such as bromocriptine, either as monotherapy or as combination therapy with levodopa. According to the Canadian guidelines on PD, a non–ergot-derived DA should be preferred to an ergot-derived DA in most cases, due to the risk of pleuropulmonary and cardiac-valve fibrosis related to the use of the latter. DAs are commonly used in early PD while restricted in older patients over the age of 70.[5] Similar to levodopa, the common AEs associated with DAs include nausea, vomiting, sleepiness, orthostatic hypotension, confusion, and hallucinations; when used long term, DAs are associated with the development of impulse-control disorders such as pathologic gambling, compulsive sexual behaviour, or compulsive buying in up to 50% of patients.[6] Apomorphine is another non-ergot DA. Its role as an add-on therapy when other anti-parkinsonian drugs have not controlled the existing motor fluctuations has been demonstrated.[11] Apomorphine can be administered through a variety of routes, including subcutaneous; transdermal, nasal, or pulmonary; sublingual; or rectal routes.[10,11] APO SC (Movapo) was reviewed by CDR in 2017 and was recommended for reimbursement as an adjunctive therapy for coping with OFF episodes for patients who are receiving optimized PD therapy.[12]

MAO-B inhibitors, such as rasagiline and selegiline, prevent the metabolism of dopamine in the brain. COMT inhibitors, such as entacapone, increase the bioavailability of levodopa in the periphery. Anticholinergics, such as trihexyphenidyl and benztropine, are mostly used in patients with tremor; their lack of effectiveness and neuropsychiatric side effects limit their use in older patients.[5] Amantadine, as monotherapy or as combination therapy with anticholinergic drugs and with levodopa, is indicated for the treatment of PD. Common AEs related to amantadine include nausea, dizziness, and insomnia, while orthostatic hypotensive episodes, congestive heart failure, depression, psychosis, urinary retention, convulsions, reversible leukopenia and neutropenia, and abnormal liver functions are important AEs.[16]

Continuous enteral infusion of levodopa plus carbidopa in a gel formulation and deep-brain stimulation are invasive treatment options for patients with inadequate management of motor complications by optimized standard therapies.[5] However, patient selection, side effects associated with these invasive approaches, uncertain long-term motor benefits, and costs are barriers for their widespread use. Therefore, the optimization of oral anti-PD medications remains the most common treatment option, particularly among advanced PD patients, with the constant challenge being to ensure an adequate plasma dopamine level and management of symptoms during unpredictable or drug–wearing OFF episodes.

Drug

Apomorphine is a non-ergot DA with high in vitro binding affinity for the dopamine D_4 receptor and moderate affinity for the dopamine D_2, D_3, and D_5, and adrenergic alpha$_{1D}$, alpha$_{2B}$, alpha$_{2C}$ receptors; its mechanism of action as a treatment for OFF episodes associated with PD is believed to be due to the stimulation of post-synaptic dopamine D_2–type receptors within the caudate-putamen in the brain.[17] Kynmobi is APO SL film. It was first submitted to CADTH for a pre-NOC review in February 2019. The proposed indication was for the acute, intermittent treatment of hypomobility and OFF episodes associated with PD, including end-of-dose wearing OFF (including early-morning OFF); partial, delayed, or no ON episodes; and unpredictable OFF. [redacted]. Therefore, the sponsor withdrew its application from the CDR process and CDEC did not review this drug. In June 2020, the sponsor refiled the submission to CADTH after APO SL received an NOC from Health Canada on June 12, 2020. The Health Canada–approved indication is for acute, intermittent treatment of OFF episodes in patients with PD.[13] The reimbursement criteria for APO SL film requested by the sponsor is the same as the Health Canada–approved indication.

APO SL is available as 10 mg, 15 mg, 20 mg, 25 mg, and 30 mg sublingual films. The recommended starting dose of APO SL film is 10 mg when the patient is in an OFF state. When the patient tolerates the dose but does not respond adequately (does not turn ON), the patient should resume their usual PD medication and up-titrate the dose of APO SL at the next observed OFF period, generally within 3 days. Titration can be continued in a similar manner in 5 mg increments until an effective and tolerable dose is achieved, up to 30 mg. Doses should be separated by at least 2 hours, and treatment should not exceed 5 films per day. The total daily dose should not exceed 90 mg.[14]

Table 3 provides details regarding the mechanism of action, indication, route and dose of administration, and side effects of apomorphine and other non-ergot DAs.

Table 3: Key Characteristics of Apomorphine, Rotigotine, Ropinirole, and Pramipexole

Characteristic	Apomorphine	Rotigotine	Ropinirole	Pramipexole
Mechanism of action	Non-ergot DA believed to stimulate D_2 receptors of the caudate-putamen.	Non-ergot DA believed to increase the activities of the D_3, D_2, and D_1 receptors of the caudate-putamen.	Non-ergot DA believed to stimulate the D_2 receptors of the caudate-putamen.	Non-ergot DA believed to stimulate the D_2 receptors of the caudate-putamen.
Indication[a]	APO SL (Kynmobi): Acute, intermittent treatment of OFF episodes in patients with PD. APO SC (Movapo): Acute, intermittent treatment of hypomobility and OFF episodes (end-of-dose wearing OFF and unpredictable ON or OFF episodes) in patients with advanced PD.	Treatment of signs and symptoms of idiopathic PD. Can be used both as early therapy without concomitant levodopa and as an adjunct to levodopa.	Treatment of signs and symptoms of idiopathic PD. Can be used both as early therapy without concomitant levodopa and as an adjunct to levodopa.	Treatment of signs and symptoms of idiopathic PD. Can be used both as early therapy without concomitant levodopa and as an adjunct to levodopa. Symptomatic treatment of moderate to severe idiopathic restless legs syndrome.

Characteristic	Apomorphine	Rotigotine	Ropinirole	Pramipexole
Route of administration	Sublingual (Kynmobi) or subcutaneous (Movapo)	Transdermal	Oral	Oral
Recommended dose	APO SL (Kynmobi): The drug is administered intermittently as needed. The initial recommended dose is 10 mg with titration up to a maximum dose of 30 mg; ≤ 5 doses per day. APO SC (Movapo): Should be initiated with the use of a concomitant antiemetic. The antiemetic should be started ≥ 2 days prior to the initial dose of Movapo. 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).	Early-stage PD: A single daily dose should be initiated at 2 mg per day and then increased in weekly increments of 2 mg per day to an effective dose up to a maximum dose of 8 mg per day. Advanced-stage PD: A single daily dose should be initiated at 4 mg per day and then increased in weekly increments of 2 mg per day to an effective dose up to a maximal dose of 16 mg per day.	The recommended starting dosage is 0.25 mg 3 times daily. Based on individual patient response, dosage should then be 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 maximum daily dose for patients without dialysis is not specified in the product monograph; however, in clinical trials, a dose of 24 mg per day was the target maximum. The recommended maximum dose is 18 mg per day in patients receiving regular dialysis. Patients with severe renal impairment (creatinine clearance less than 30 mL per minute without regular dialysis) have not been studied and administration of ropinirole to such patients is not recommended.	Dosages should be increased gradually from a starting dose of 0.375 mg per day given in 3 divided doses and should not be increased more frequently than every 5 to 7 days. The maximum recommended dose is 4.5 mg per day. In patients with a creatinine clearance of between 30 mL per minute and 50 mL per minute, the initial daily dose should be administered in 2 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 per minute and 30 mL per minute, 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 or safety issues	Warnings or precautions: Sudden onset of sleep and somnolence.	Warnings or precautions: Sudden onset of sleep.	Warnings or precautions: Sudden onset of sleep.	Warnings or precautions: Sudden onset of sleep and somnolence.

APO = apomorphine hydrochloride; DA = dopamine agonist; PD = Parkinson disease; SC = subcutaneous; SL = sublingual.

[a] Health Canada indication.

Sources: Product monographs for Kynmobi (apomorphine),[14] Movapo (apomorphine subcutaneous injection),[18] Neupro (rotigotine),[19] Requip (ropinirole),[19] and Mirapex (pramipexole).[20]

Stakeholder Engagement

Patient Group Input

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

About the Patient Groups and Information Gathered

Five patient groups submitted input for this review. Each organization supports those affected by PD in the form of information and funding for programs aimed at improving quality of life or innovative research to develop treatments or both, and to find a cure for PD. A brief description of each organization follows.

The Michael J. Fox Foundation is a non-profit organization dedicated to accelerating a cure for PD and improved therapies. It collaborates with industry leaders, academic scientists, and government research programs; increases the flow of participants into PD trials; promotes PD awareness; and coordinates the grassroots involvement of its members around the world (www.michaeljfox.org).

The Parkinson Association of Alberta is a charitable organization that provides services in 3 areas: support (mental, emotional, and peer), education (information, resources, referrals, and webinars) and active (physical, speech, and swallowing, cognitive, and social) programs to the more than 10,000 Albertans with PD and Parkinson-plus syndromes, their families and care partners, health care professionals, community partners, and the public. It relies on donations and fundraising (parkinsonassociation.ca).

Operating since 1965, Parkinson Canada is a national registered charity sustained by donations. It advocates on behalf of the PD community and provides support services and education to people living with PD and their care partners, families, and health care professionals (www.parkinson.ca).

Established in 1969, Parkinson Society British Columbia is a non-profit organization governed by a volunteer board of directors. The Society is supported entirely by donations from individuals, members, corporations, foundations, and volunteers. The organization offers support, shares information, and raises funds for programs and research for all those touched by PD (www.parkinson.bc.ca).

Parkinson Québec is a non-profit organization supporting the 25,000 Quebecers living with PD and their families. It focuses on 3 areas: service development, advocacy, and research funding; revenue development; and communication and network management (https://parkinsonquebec.ca).

Each organization provided the source(s) of the information contained in its submissions. The Michael J. Fox Foundation cited its guide for people navigating PD (*Parkinson's 360º*) as the primary source for its submission content. The guide draws on both expert and patient experiences. The secondary sources were the foundation's website and a 2014 survey of more than 3,000 patients with PD regarding ON and OFF episodes. The Parkinson Association of Alberta gathered perspectives through an online survey (conducted from March 9 to 15, 2019) that was distributed to the Parkinson community across Alberta and beyond. It also reached out to clients again in June 2020 to enrol additional respondents. Of the 61 responses, all but 2 (from Ontario) were Albertans: 74% of respondents were people with PD, and 26% were caregivers or family members.

Parkinson Canada conducted 3 surveys between June 2017 and December 2018, generating 853, approximately 1,500, and 50 responses, respectively. Between 97% and 100% of respondents were Canadians from most provinces (a few were from the territories); the vast majority were either Canadians diagnosed with PD or their caregivers. The 2 large surveys addressed living with PD, access to care and treatment, disease management, and so forth, while the smaller survey specifically sought feedback on Kynmobi. Parkinson Canada also connected with 5 patients who had experience using apomorphine (injectable or pump). Parkinson Society British Columbia cites as its sources a previous submission to CADTH in 2017 (Movapo), and a survey conducted from February to March 2019 among the British Columbia Parkinson community that generated responses from 46 patients and 19 caregivers. Parkinson Québec gathered patient input through an online survey conducted from February to March 2019. Survey respondents included Québec patients living with PD who had experienced at least 1 OFF episode in the past month and their caregivers. In total, 292 patients and 78 caregivers responded to the survey. Verbatim comments specific to patient's OFF-period experiences were also gathered through phone interviews.

Disease Experience

Although motor symptoms are the most prominent indication of PD and it is classified as a disorder of movement, PD is a heterogeneous condition and encompasses a large number of motor and non-motor symptoms experienced by each patient to different degrees, from mild to severe, or not at all. Disease onset is typically after 50 years of age, but 5% to 10% of cases occur earlier. Some patients will experience a normal life expectancy with little symptom evolution over 20 years, while others will endure a much more rapid progression. Early diagnosis and treatment may help slow progression, but accurate diagnosis can be challenging, as many pre-diagnosis symptoms are non-motor and non-specific, such as depression and anxiety, sleep disturbances, and constipation.

Early-stage disease symptoms may affect a patient's ability to work, socialize, exercise, eat, sleep, and perform daily tasks. Mid- and late-stage disease often involves speech impairment, hypophonia, swallowing problems, drooling, poor stomach emptying, flexed or bent posture, postural instability, rigidity in neck and trunk, motor fluctuations, and dyskinesia, which can progress into more severe walking problems, instability, shuffling, festination, and freezing of gait. PD psychosis or dementia can occur in later stages. Some symptoms, especially those related to involuntary movements, difficulties swallowing, and the stomach or gut can become severe enough to affect food and medication delivery to, and uptake by, the body. These problems can exacerbate the patient's condition. People with PD are at increased risk of choking, falling or injury, malnutrition, fatigue, depression, and aspiration pneumonia. Patients may require interventions such as counselling; physical, occupational, swallowing, or speech therapies; assisted walking devices or wheelchairs; insertion of a feeding tube or catheter; and use of a number of medications to control the various symptoms. Over time, patients may require palliative care in a clinic, assisted living or nursing centre, or an intensive care unit.

Almost half of respondents felt their family and social relationships were negatively impacted by the disease and a large majority had experienced a loss in quality of life and ability to participate in recreational activities and exercise. A subset of respondents also discussed having to leave the workforce or reduce their employment hours. Others described the disease as "devastating." Throughout the patient group submissions,

common threads of isolation, exhaustion, and frustration were apparent, especially in the context of symptom and medication management.

Overwhelmingly, people with PD describe a “loss of confidence” or “loss of independence” since developing the disease: “It is increasingly more challenging to manage care of myself, dog, & home. Also attending the local Parkinson’s exercise group, and other activities is becoming more limited. Because of my Parkinson’s tremor, even with medication, I have lost my confidence in any social situations where food is served, and so no longer want to participate in these activities.”

From the caregiver’s perspective, the role can be a very fulfilling experience; many caregivers are content in their roles and states of health. However, as their loved one’s disease progresses, the challenges can become numerous. Care partners are often faced with emotional, physical, and financial stresses that can strain the relationship and lead to fatigue, depression, burnout, and illness. They may have to sacrifice their careers or abandon their social lives as the demands on their time increase.

A large amount of information was provided relating to Parkinson symptoms and disease conditions, beyond what can be presented in this summary. All of the information from the patient input submissions for Kynmobi can be downloaded on our website at https://cadth.ca/apomorphine-hydrochloride-0.

Experience With Treatment

In the early stages, lifestyle changes and healthy living may suffice for disease management. People with PD may benefit from exercise or rehabilitation therapies and may not need medication. However, as the disease progresses, most patients will likely use 1 or multiple medications, different forms of therapy (e.g., physiotherapy, occupational therapy, speech therapy, exercise, or psychological therapy), and may require surgical interventions.

The main and most effective treatment for PD is levodopa. Levodopa has been used for decades to treat the major motor deficits. Almost all people with PD will take this drug at some point during their disease management. While it is the most effective medication for the treatment of motor symptoms, with the fewest short-term side effects, paradoxically, levodopa poses a higher risk of long-term side effects and motor complications. Other classes of drugs are used in conjunction with, and sometimes instead of, levodopa to help control motor symptoms, yet other medications are prescribed to address the numerous non-motor symptoms that may arise.

The nature of PD treatments leads to 2 states experienced during the day: ON (a state during which motor symptoms are controlled by medication) and OFF (a state which can occur gradually between doses when the medication is wearing off, or can arise quickly and unpredictably). These daily fluctuations are experienced by the large majority of those with PD and can occur on any medication. Patient groups conducted surveys specific to ON-OFF fluctuations. They found that 90% of respondents had at least 1 daily ON-OFF fluctuation, and nearly half of respondents had moderate to severe OFF episodes. As the disease progresses, patients treated with levodopa may experience increased dyskinesia (a motor complication as medication peaks during the ON state) and longer times spent in the OFF state (loss of medication effectiveness). The OFF state is associated with a much higher degree of disability and loss of confidence than the ON state. It has been described by some patients as terrifying and life-threatening. Patients may suddenly lose the ability to swallow or breathe; they may lose their balance or collapse. Generally, survey respondents

reported ongoing challenges managing the OFF times. As PD progresses, patients require more frequent and higher concentrations of medication. Managing side effects and timing of delivery becomes a challenge. Levodopa should not be taken with food containing protein and many patients experience difficulty eating their meal quickly. With increases in the frequency of medication intake, timing becomes more difficult to manage and to remember. These challenges can be exacerbated by the onset of symptoms during the OFF state (such as tremors, difficulty swallowing, cognition deficits) and medication side effects (such as dyskinesia, nausea, constipation, exhaustion).

There is an unmet need among people with PD for medications that offer better symptom control with fewer side effects and for add-on therapies that provide a "grace period" during the OFF state. Injectable apomorphine and surgical interventions are treatment options for OFF episodes. Both of these treatments can be effective, but they are invasive options with limited windows of opportunity and potential side effects such as nausea, vomiting, painful nodules under the skin, or surgical complications. Other unmet needs discussed in the Canadian context revolve around: the expense of treatments; timely access to neurologists and long wait times before prescriptions can be adjusted; access to and cost of various forms of therapy (rehabilitation, psychological); transportation and travel burdens; lack of access to "in stock" and brand medications; storage of medication; formulation of medication and forms of delivery; lack of medication for treatment of cognitive issues; and the time required to manage symptoms and side effects, attend appointments, pick up medication, and so forth.

The patient groups that responded to this call for input did not have experience with APO SL. Some reported patient experiences with injectable or pump apomorphine with mixed results, from discontinuation of drug, to improved quality of life, to positive life changing.

Improved Outcomes

Patients who experience OFF episodes are looking for medications that can provide relief during these troublesome or debilitating periods of the day. Injectable apomorphine is an option. It can be an effective therapy for some, but it may be under-prescribed and underused due to unpleasant or unacceptable side effects, contraindication due to the patient's condition(s) or current medication regime, and difficulties experienced trying to inject the medication while suffering from motor symptoms brought on by the OFF state.

The following patient quote provides insight into the patient expectation for the new treatment: "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."

Among the groups' survey results, a range of 40% to 93% of respondents favoured a sublingual form of apomorphine. There is hope that sublingual delivery will be more convenient, more tolerable (fewer side effects) and more effective than the injectable format.

Clinician Input

All CADTH review teams include at least one clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol; assisting in the critical appraisal of clinical evidence; interpreting the clinical relevance of the results and providing guidance on the potential place in therapy). The following input was provided by one clinical specialist with expertise in the diagnosis and management of PD.

Unmet Needs

Currently available medical therapies for PD are symptomatic therapies, that is, they treat the symptoms and the disability suffered by the patient. Most expert guidelines and recommendations review treatment in motor and non–motor symptom categories.

Motor symptoms are the movement problems caused by PD, including tremor, bradykinesia, rigidity, gait difficulty, as well as effects on motor functions like chewing, swallowing, and speech. Non-motor symptoms include sleep disorders, cognitive and neuropsychiatric symptoms, autonomic nervous system dysfunction, sensory symptoms, and pain.

Treatment of motor disability (e.g., motor symptoms that prevent completion of daily activities) is usually a key treatment target. As disease progresses, the need for treatment and the manner in which treatment works for motor symptoms evolves: treatment effects become shorter and more unreliable, and patients spend more waking hours with functional impairment, including nighttime and early-morning symptoms.

Place in Therapy

Most available medical therapies for motor symptoms have a delayed clinical effect, and APO SL (Kynmobi) works quickly. This provides a tool that patients can apply for a short-term effect on motor symptoms, as is needed with the sudden, unexpected emergence of symptoms, symptoms that emerge in the night when oral medication scheduling is not practical, and ineffective or partially effective oral medication doses.

Patient Population

In the expert's opinion, patients who frequently (i.e., more than once per week) find themselves suddenly or urgently in need of treatment for motor symptoms despite attempts at optimizing oral medications, should or will receive APO SL in practice. For instance, patients experiencing OFF episodes or a sudden need for motor-symptom treatment despite 5 or more doses of oral medication per day. These episodes may occur overnight or early in the morning, either from an ineffective dose or as a feature of complex motor fluctuations.

Clinical Evidence

The clinical evidence included in the review of Kynmobi is presented in 3 sections. The first section, the systematic review, includes pivotal studies provided in the sponsor's submission to CADTH and Health Canada, as well as those studies that were selected according to an a priori protocol. The second section includes indirect evidence from the sponsor and indirect evidence selected from the literature that met the selection criteria specified in the review. The third section includes sponsor-submitted long-term extension studies and additional relevant studies that were considered to address important gaps in the evidence included in the systematic review.

Systematic Review (Pivotal and Protocol Selected Studies)

Objectives

To perform a systematic review of the beneficial and harmful effects of APO SL film (Kynmobi) for the acute, intermittent treatment of OFF episodes in patients with PD.

Methods

Studies selected for inclusion in the systematic review include pivotal studies provided in the sponsor's submission to CDR, as well as those meeting the selection criteria presented in Table 4.

Table 4: Inclusion Criteria for the Systematic Review

Patient population	Adult patients with PD Subgroups: • baseline severity of PD • background oral medications for PD • type of OFF episodes (e.g., wearing OFF, partial OFF, delayed OFF, no ON, or unpredictable OFF)
Intervention	APO SL film: • 10 mg to 30 mg per dose (starting dose: 10 mg at an OFF state; increase the dose to the next dose strength at the next observed OFF period, titrated up to a maximum of 30 mg per dose) • no more than 5 doses per day and doses should be separated by ≥ 2 hours • added to background oral medications for PD
Comparators	Placebo added to oral medications for PD used as monotherapy or combination therapy: • levodopa plus carbidopa or levodopa plus benserazide[a] (with or without COMT inhibitors, e.g., entacapone, tolcapone) • dopamine agonists (e.g., bromocriptine, pramipexole, ropinirole, rotigotine transdermal patch) • MAO-B inhibitors (e.g., selegiline, rasagiline) • amantadine APO SC injection as an adjunct to regular anti-PD medications

Outcomes	**Efficacy outcomes** • Mobility (or hypomobility) by validated measure (e.g., change from pre-dose in MDS-UPDRS scores at study end point) • Duration of OFF episodes (e.g., duration of each OFF episodes, sum of time of OFF episodes per day)[b] • Frequency of patient-rated ON or OFF episodes[b] • Symptom reduction (e.g., tremor, bradykinesia, rigidity, and postural instability, sleep disturbance) [b] • HRQoL measured with a validated instrument[b] • Patient satisfaction (e.g., PGI-I) • Time to response (e.g., interval between drug administration and an observed effect) • Use of health care services (e.g., hospitalization) **Harms outcomes** AEs, SAEs, WDAEs, mortality, and notable harms and harms of special interest (dyskinesia, nausea, or vomiting, somnolence, postural hypotension, application-site reaction, impulsive behaviour, and so forth)
Study design	Published and unpublished phase III or IV RCTs

AE = adverse event; APO = apomorphine; COMT = catechol O-methyltransferase; HRQoL = health-related quality of life; MAO-B = monoamine oxidase type B; MDS-UPDRS = Movement Disorders Society Unified Parkinson's Disease Rating Scale; PD = Parkinson disease; PGI-I = Patient Global Impression—Improvement; RCT = randomized controlled trial; SAE = serious adverse event; SC = subcutaneous; SL = sublingual; WDAE = withdrawal due to adverse event.

[a] Levodopa is commonly combined with a dopa-decarboxylase inhibitor: levodopa plus carbidopa or levodopa plus benserazide.

[b] Identified as an important outcome by the patient groups.

The literature search for clinical studies was performed by an information specialist using a peer-reviewed search strategy according to the *PRESS Peer Review of Electronic Search Strategies* checklist (https://www.cadth.ca/resources/finding-evidence/press).[21]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) through Ovid, Embase (1974–) through Ovid, and PubMed. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Kynmobi (apomorphine hydrochloride) and PD. Clinical trial registries were searched: the US National Institutes of Health's clinicaltrials.gov and the World Health Organization's International Clinical Trials Registry Platform (ICTRP) search portal.

No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. See Appendix 1 for the detailed search strategies.

The initial search was completed on July 9, 2020. Regular alerts updated the search until the CDEC meeting on October 21, 2020.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters: A Practical Tool for Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters):[22] Health Technology Assessment (HTA) Agencies, Health Economics, Clinical Practice Guidelines, Drug and Device Regulatory Approvals, Advisories and Warnings, Drug Class Reviews, Clinical Trials Registries, and Databases (Free). Google was used to search for additional internet-based materials. These searches were supplemented by reviewing bibliographies of key papers and through contacts with appropriate experts. In addition, the sponsor of the drug was contacted for information regarding unpublished studies. See Appendix 1 for more information on the grey literature search strategy.

Two 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 1 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 5.

Findings From the Literature

A total of 1 study was identified from the literature for inclusion in the systematic review (Figure 1). The included study is summarized in Table 5.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

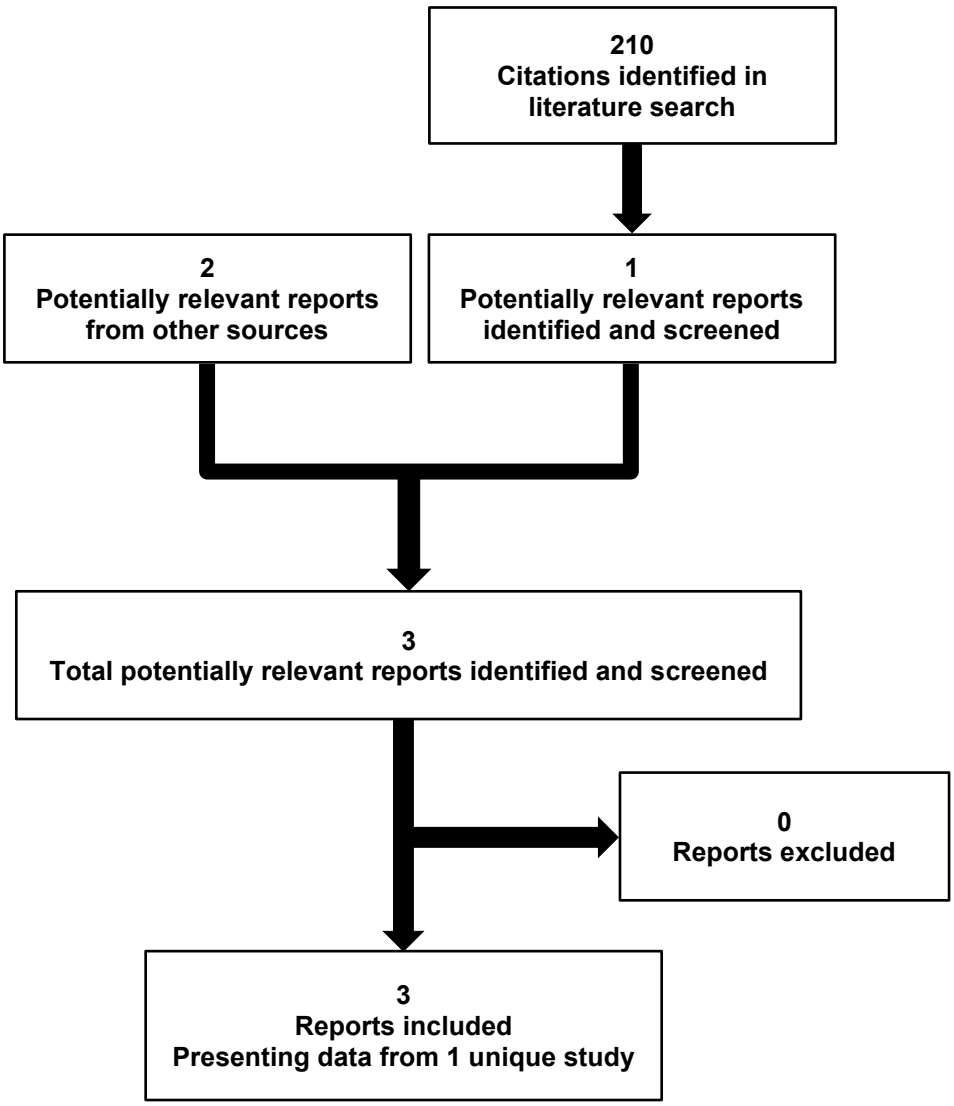


Table 5: Details of Included Studies

	Study detail	CTH-300
Designs and Populations	**Study design**	Phase III, multi-centre, DB RCT
	Locations	32 sites in the US and 1 site in Canada
	Randomized (N)	141
	Inclusion criteria	• Patients ≥ 18 years of age • Clinical diagnosis of idiopathic PD • Stages 1 to 3 on the modified Hoehn & Yahr scale in the ON state • Clinically meaningful response to levodopa with well-defined early-morning OFF episodes (investigator-determined) • ≥ 1 OFF episode per day with a total daily OFF time duration of ≥ 2 hours during the waking day (patient-reported); MMSE score > 25 • Receiving stable doses of levodopa plus carbidopa (IR, CR, or ER) for ≥ 4 weeks before study screening, or MAO-B inhibitors for ≥ 8 weeks
	Exclusion criteria	• Atypical or secondary parkinsonism • Previous treatment with neurosurgical procedure for PD, continuous APO SC infusion, carbidopa plus levodopa, APO SC ≤ 7 days prior to the initial screening • Currently taking selective 5-HT_3 antagonists, dopamine antagonists (excluding quetiapine and clozapine) or dopamine-depleting drugs • Hypersensitivity to APO, trimethobenzamide, or domperidone • Clinically significant medical, surgical, or laboratory abnormality • Major psychiatric disorders • History of clinically significant hallucinations in the past 6 months, history of clinically significant impulse-control disorder(s), dementia that precluded providing informed consent or would interfere with participation in the study • Current suicidal ideation (≤ 1 year prior to the second screening) or attempted suicide < 5 years • Cankers or mouth sores ≤ 30 days prior to the initial screening or other clinically significant oral pathology
Drugs	**Intervention**	APO SL (initial dose 10 mg titrated in 5 mg increments up to 35 mg per dose[a] and up to 5 doses per day) plus stable doses of a levodopa formulation and other stable adjunctive PD medications
	Comparator(s)	Placebo plus stable doses of a levodopa formulation and other stable adjunctive PD medications
Duration	**Phase**	
	Open-label dose titration	≤ 3 weeks
	Double-blind maintenance treatment	12 weeks
	Follow-up	1 week

	Study detail	CTH-300
Outcomes	**Primary end point**	Mean change from pre-dose in MDS-UPDRS Part III score at 30 minutes post dose at week 12 visit
	Other end points	• Percentage of patients with a patient-rated full ON response within 30 minutes post dose at week 12 visit • Mean change from pre-dose in MDS-UPDRS Part III score at 15, 45, 60, and 90 minutes post dose at week 12 visit • Time from dosing to when study drug was starting to have an ON effect at week 12 visit • Percentage of patients with a patient-rated full ON response within 30 minutes whose duration from the time when the study drug began to have an effect until OFF (if applicable) lasted for ≥ 30 minutes at week 12 visit • Post-dosing CGI-I • Post-dosing PGI-I • Symptom reduction (e.g., ESS) • HRQoL (e.g., EQ-5D and PDQ-39) • Mean change from baseline in MDS-UPDRS Part II (motor aspects of experiences of daily living) • Safety
Notes	**Publications**	Olanow et al. (2020)[23]

5-HT3 = 5-hydroxytryptamine-3; APO = apomorphine hydrochloride; CGI-I = Clinical Global Impression—Improvement; CR = controlled release; DB = double blind; EQ-5D = EuroQol 5-Dimensions questionnaire; ER = extended release; ESS = the Epworth Sleepiness Scale; HRQoL = health-related quality of life; IR = immediate release; MAO-B = monoamine oxidase type B; MDS-UPDRS = Movement Disorders Society Unified Parkinson's Disease Rating Scale; MMSE = Mini-Mental State Examination; PD = Parkinson disease; PDQ-39 = Parkinson's Disease Questionnaire 39; PGI-I = Patient Global Impression—Improvement; RCT = randomized controlled trial; SC = subcutaneous; SL = sublingual.

[a] Based on the Health Canada–approved product monograph, the maximum dose of APO SL film is 30 mg.

Note: 2 additional reports were included (CADTH Common Drug Review submission[24] and Health Canada Reviewer's Report).[25]

Source: CTH-300 Clinical Study Report.[15]

Description of Studies

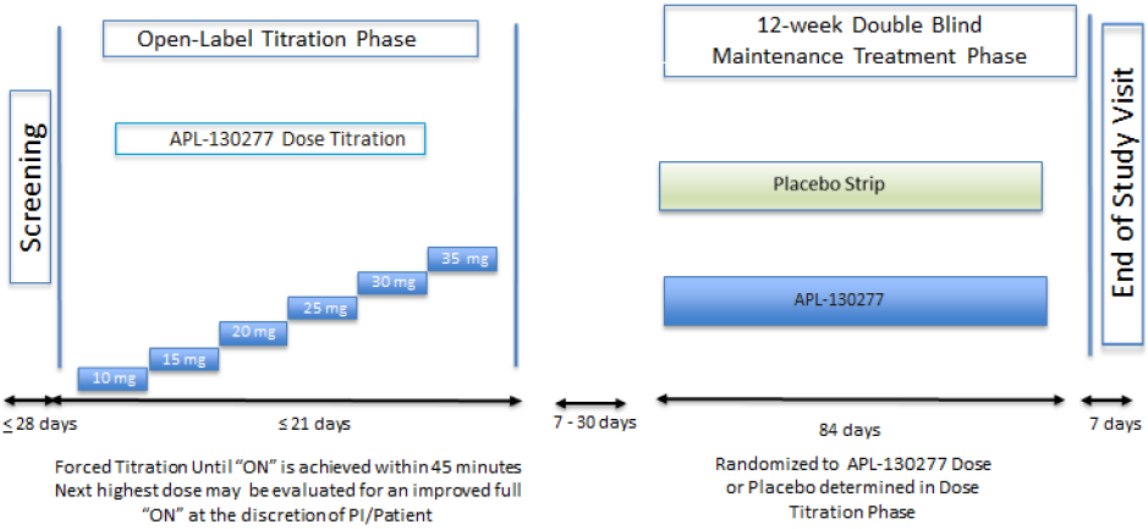
One phase III multi-centre, double-blind, superiority RCT (CTH-300) met the inclusion criteria for this systematic review.[15] The study design of CTH-300 is shown in Figure 2.

The primary objective of CTH-300 was to evaluate the efficacy and safety of APO SL versus placebo in patients with PD over a 12-week period. The study contained 2 phases. In the open-label dose titration phase, the patient's response to a single, escalating dose of APO SL was evaluated in an outpatient setting to determine the dose that would be used in the next phase, a double-blind maintenance treatment phase. The dose titration phase was limited to 3 weeks. After the completion of the dose titration phase, study participants who responded to a specific dose of between 10 mg and 35 mg (i.e., achieved a full ON response within 45 minutes of drug administration) and tolerated the adverse effects entered the 12-week dose maintenance phase. Between the last day of the titration phase and the first day of the maintenance treatment phase, there was a 7- to 30-day period. The rationale for including this period in the trial was not explained. It could be a washout period for the patients before randomization. Eligible participants were randomized centrally at a study level, using a computer-generated randomization code via an interactive web response system (IWRS), to treatment with APO SL (at the dose reached during titration) or placebo at a 1:1 ratio. There were no stratification factors used in the randomization. The patients returned to the clinic in 4-week intervals for safety and efficacy assessments. Throughout

the maintenance treatment phase, the patients and all clinical site personnel remained blinded to the treatment assignment. The investigators did not have access to the randomization code except in case of an SAE. If AEs occurred and unblinding was required, the investigator would disclose the treatment assignment from the IWRS system. One week following the completion of the study, patients were asked to return for a final safety assessment visit. The primary efficacy end point was the mean change in the MDS-UPDRS III score from pre-dose to 30 minutes post dose at the week 12 visit.

Two external committees were involved in the study. Prior to enrolling patients in the study, the enrolment adjudication committee (EAC), made up of 2 neurologists, determined the potential study participant's appropriateness for inclusion in the study, independent of the entry criteria. Following EAC approval, the final determination of eligibility for enrolment in the study was made by the investigator. A data safety monitoring board reviewed data on a regular basis during the study, determined the appropriateness of the study to continue based on the safety profile, and evaluated whether potential changes to the safety assessment schedule should be implemented.

Figure 2: Study Design of CTH-300



PI = principal investigator.

Source: CTH-300 Clinical Study Report.[15]

Populations

Inclusion and Exclusion Criteria

Adult patients with idiopathic PD (consistent with the Parkinson's UK Brain Bank criteria), classified as stages 1 to 3 in the modified Hoehn & Yahr scale, with a clinically meaningful response to treatment with levodopa and with at least 1 OFF episode per day were included. Patients were required to be on stable anti-PD treatments prior to study screening, at least 4 weeks for levodopa-related therapy or 8 weeks for MAO-B inhibitors. In Study CTH-300, potential participants must have been pre-approved as a satisfactory candidate by an external committee (the EAC). The role of the EAC was to determine the patient's appropriateness for inclusion in the study based on the patient's disease characteristics, such as duration of PD, stage on the Hoehn & Yahr scale, response to

levodopa therapy, MDS-UPDDRS Part III score, duration of OFF time per day, history of significant psychiatric problems, concomitant medications, and side effects from previous or concomitant drug therapy.

Patients were excluded if they had any of the following: atypical or secondary parkinsonism; were receiving or had received medication or therapy that could confound the interpretation of the study results or be a safety risk if taken concomitantly with the study drug; a clinically significant medical, surgical, or laboratory abnormality that might jeopardize the patient's safety or affect the patient's adherence to the study drugs (e.g., major psychiatric disorders, dementia, or suicidal ideation); cankers, mouth sores, or other clinically significant oral pathology within 30 days prior to the initial screening.

Details of the selection criteria in CTH-300 are presented in Table 5.

Baseline Characteristics

Patient characteristics in the mITT population overall were similar between treatment groups except for the percentage of males and females. The participants had a mean age of 63 years, were predominantly male (males: 69% in the APO SL group versus 56% in the placebo group) and White (93%). Patients had a mean duration of PD of 9 years at baseline; therefore, the age of onset was around 54 years. Patients had experienced motor fluctuations for approximately 5 years. They reported an average of 4 OFF episodes per day, and each OFF episode lasted about an hour. The daily levodopa dose at baseline was similar between the groups, ranging from 1,058 mg in the APO SL group to 1,007 mg in the placebo group. The average pre-dose MDS-UPDRS Part III scores were 43 in both treatment groups. The patient characteristics in the safety population were similar to those in the mITT population, although patients in the safety population tended to be older and took more levodopa per day.

In terms of concomitant anti-PD medications, all patients (100%) in the safety population were taking levodopa and dopa-derivative PD medication, with the other most common PD medications being DAs (56.0%), MAO-B inhibitors (42.2%), and amantadine derivatives (22.0% in total; 15% with APO SL versus 29% with placebo).

Details of patients' demographic and baseline characteristics in Study CTH-300 are presented in Table 6.

Table 6: Summary of Baseline Characteristics in Study CTH-300 (Safety Population and mITT[a] Population)

Baseline characteristic	Safety population (N = 141)	mITT population	
		APO SL (N = 54)	Placebo (N = 55)
Age (years), mean (SD)	[redacted]	62.9 (9.79)	62.5 (8.12)
Gender, n (%)			
Male	[redacted]	37 (68.5)	31 (56.4)
Female	[redacted]	17 (31.5)	24 (43.6)
Race, n (%)			
Asian	[redacted]	4 (7.4)	1 (1.8)
Black or African American	[redacted]	0	2 (3.6)
Native Hawaiian or other Pacific Islander	[redacted]	0	1 (1.8)

Baseline characteristic	Safety population (N = 141)	mITT population	
		APO SL (N = 54)	Placebo (N = 55)
White	[redacted]	50 (92.6)	51 (92.7)
BMI (kg/m^2), mean (SD)	[redacted]	[redacted]	[redacted]
Time since diagnosis of PD (years), mean (SD)	[redacted]	8.7 (4.25)	9.3 (3.84)
Time since motor fluctuations started (years), mean (SD)	[redacted]	4.69 (3.92)	4.54 (3.78)
Type of OFF episodes, n (%)			
Morning akinesia	[redacted]	46 (85.2)	44 (80.0)
Wearing OFF	[redacted]	54 (100)	54 (98.2)
Delayed ON	[redacted]	29 (53.7)	43 (78.2)
Dose failure	[redacted]	22 (40.7)	23 (41.8)
Sudden OFF	[redacted]	26 (48.1)	32 (58.2)
Number of OFF episodes per day, mean (SD)	[redacted]	3.9 (1.17)	3.8 (1.40)
Typical length of OFF episodes (minutes), mean (SD)	[redacted]	63.7 (31.91)	66.1 (30.09)
Total daily levodopa dose (mg), mean (SD)	[redacted]	1,058.70 (563.30)	1,007.73 (562.32)
Patients with ≥ 1 concomitant anti-PD medication, n (%)			
levodopa and dopa derivatives	[redacted]	54 (100)	55 (100)
Dopamine agonists	[redacted]	30 (55.6)	31 (56.4)
MAO-B inhibitors	[redacted]	22 (40.7)	24 (43.6)
Amantadine derivatives	[redacted]	8 (14.8)	16 (29.1)
Pre-dose MDS-UPDRS Part III score, mean (SD)	[redacted]	43.2 (15.17)	43.1 (14.38)

APO = apomorphine hydrochloride; BMI = body mass index; MAO-B = monoamine oxidase type B; MDS-UPDRS = Movement Disorders Society Unified Parkinson's Disease Rating Scale; mITT = modified intention to treat; PD = Parkinson disease; SD = standard deviation; sublingual.

[a] mITT population included all patients who were randomized and received at least 1 dose of the study drug.

Source: CTH-300 Clinical Study Report.[15]

Demographic characteristics and baseline PD history for patients included in the safety population but not randomized to treatment in the maintenance treatment phase (for example, enrichment failures, N = 32) were compared with the mITT population (data not shown). Compared with the mITT population, the enrichment failure group was relatively older, experienced more OFF episodes and a longer duration of OFF each day, had a shorter time since PD diagnosis, and took more levodopa. Overall, the differences observed between the mITT population and the enrichment failure group were not considered clinically significant by the investigators.

Interventions

After screening, eligible patients entered the dose titration phase, where patients' responses to escalating single doses of APO SL were evaluated to determine the optimal dose of APO SL that would be used in the maintenance phase of the study for treating OFF episodes. In the morning of the first day of titration, patients attended the clinic without taking their normal morning PD medications. The dose of APO SL was started at 10 mg

and could be adjusted in 5 mg increments within the next 3 days. The maximum dose was 35 mg. On the contrary, the maximum dose indicated in the drug product monograph is 30 mg. If, at a specific dose level, the patients achieved a full ON state within 45 minutes of drug administration, the dose titration phase was considered complete; the patients then proceeded to randomization and the maintenance treatment phase of the study at this dose. If the patients did not show improvement in OFF state with a particular dose, they were required to return to the clinic within the next 3 days to assess the next higher dose of APO SL. If the patients could not tolerate the OFF state and did not respond efficaciously to the investigating dose of APO SL, they were terminated from the study. Any patients who reached 35 mg at the last titration visit (the sixth visit) and did not exhibit a full ON response within 45 minutes were terminated from the study. The dose titration was required to be completed within 21 days. During the dose titration phase visits, patients were allowed to receive rescue levodopa (with or without other adjunctive PD medication) at their standard dosage, or at a dosage considered appropriate by the investigator to achieve a full ON state if, in the opinion of the investigator, the patients could no longer tolerate the OFF state at any point during the visit. At the discretion of the patient or investigator, the next highest dose could be evaluated at a subsequent titration visit following a full ON response in order to assess the potential for the next highest dose in inducing an improved full ON response. If this dose produced an improved ON response relative to the lower dose without impacting patient safety and tolerability, the higher dose was used during the maintenance treatment phase of the study. If the ON response was the same or worse, or this higher dose was not well tolerated, the previous dose was used during the maintenance treatment phase of the study. During the first titration visit, patients received training on handling the SL films using a placebo film.

Following completion of the titration phase, patients were randomized to either APO SL or placebo and began the double-blind maintenance treatment phase. There were no stratifications in randomization. The strength of the self-administered treatment (APO SL or placebo) ranged from 10 mg to 35 mg per dose, and up to 5 doses were allowed per day, separated by at least 2 hours. The study medications could be administered by the patients or their caregivers at home. If, at any time during the maintenance treatment phase, it was determined that a dose adjustment was required for the patient's safety, the patient returned to the clinic for an unscheduled dose adjustment visit and the dose could be reduced to the next lower level. If, in the opinion of the investigator, a reduced dose would not be tolerated by the patient, they were discontinued from the study, which implies that more than 1 dose reduction was not allowed. Increase in dosage was not allowed in CTH-300.

A dose of 35 mg was given as 2 APO SL films consisting of a 20 mg dose followed by a 15 mg dose. To maintain blinding, the placebo sublingual films were identical to the APO SL film in size, shape, colour, and appearance but contained no active ingredient. It is unknown whether the films were different in taste.

Concomitant stable doses of levodopa with or without other stable adjunctive PD therapies (administered at least 4 weeks prior to the initial screening visit with no planned medication changes during the study) were allowed throughout the study. MAO-B inhibitors were allowed but had to be stable for at least 8 weeks prior to the initial screening visit. Anti-nausea medication (trimethobenzamide 300 mg 3 times daily or domperidone 10 mg twice daily) was administered for 3 days prior to titration. Use of anti-nausea medication was required during the dose titration phase but could be discontinued during the maintenance treatment phase at the discretion of the investigator.

Outcomes

Mobility or Hypomobility by Validated Measures

The change in the MDS-UPDRS Part III (motor examination, measuring hypomobility) score from pre-dose to 30 minutes post dose was the primary efficacy outcome in CTH-300. The MDS-UPDRS Part III score was also measured at additional time points (e.g., 15, 45, 60, or 90 minutes post dose). The MDS-UPDRS is a widely used tool to measure disease severity, progression, and treatment response in PD patients and consists of 4 parts. MDS-UPDRS Part III (motor examination) comprises 18 items designed to assess speech, facial expression, rigidity, tremors, finger tapping, hand movements, 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).[26,27] The MDS-UPDRS was performed by the principal investigator or an appropriately trained, certified site staff member. The MDS-UPDRS Part III has been shown to have acceptable validity and reliability. MCIDs of −3.25 points for detecting minimal but clinically meaningful improvement and 4.63 points for observing minimal but clinically meaningful worsening were reported in a mixed PD population in which all disease severity levels were included.[26]

Assessment of ON and OFF States

In CTH-300, various approaches were used to measure ON and OFF states, such as duration of OFF episodes (e.g., duration of each OFF episode, sum of duration of OFF episodes per day) or frequency of patient-rated ON or OFF episodes.

A full ON episode, as assessed by the patient, was defined as a period of time during which medication was providing benefit with regard to mobility, stiffness, and slowness, where a patient felt they could perform normal daily activities, and where the response was comparable to or better than their normal response to PD medications prior to enrolling in the study. Patient diaries were used to record information about ON and OFF episodes (e.g., frequency, duration, time to onset, number of films, and recovery from perceived OFF episodes). In CTH-300, patients were trained to recognize both ON and OFF states, and trained in the completion of the diaries. When assessed by the investigator, a full ON was defined according to clinical judgment, the period of time where the investigator felt the medication was providing benefit with regard to mobility, stiffness, and slowness, and the patient had adequate motor function to allow them to perform their normal daily activities.

The percentage of patients with a patient-rated full ON response within 30 minutes post dose at week 12 was a key secondary efficacy outcome in CTH-300. The percentage of patients with a full ON response within 30 minutes post dose that lasted at least 30 minutes at week 12 was a secondary efficacy outcome. Evaluation of these outcomes was based on patient assessment at the study visits but not on diaries. Both outcomes were included in the hierarchical statistical testing.

Symptom Reduction

Daytime sleepiness is a common feature of a variety of disorders, including PD. The ESS is a self-administrated questionnaire that is frequently used in studies involving patients with PD to evaluate daytime sleepiness.[28] The patients rate the chance of dozing off in 8 different situations: sitting and talking to someone; in a car, while stopped for a few minutes in traffic; sitting inactively in a public place; sitting quietly after lunch without alcohol; as a passenger in a car for 1 hour without a break; sitting and reading; watching TV; and lying down to rest in the afternoon when circumstances permit. The response options

range from 0 (would never doze) to 3 (high chance of dozing), and yield a total ESS score between 0 and 24. A higher score indicates more severe sleepiness. An MCID for the ESS was not identified from the literature. In general, scores greater than 10 are considered indicative of excessive sleepiness.[28,29] Change from baseline in ESS total score at week 12 was a secondary end point in CTH-300; however, it was not part of the hierarchical analysis plan.

Health-Related Quality of Life

In CTH-300, HRQoL was measured using both disease-specific and generic instruments.

Parkinson's Disease Questionnaire 39

The PDQ-39 is a disease-specific, self-administered tool developed to measure the impact of PD on HRQoL. Thirty-nine questions are grouped into 8 domains: mobility (10 items), activities of daily living (ADL) (6 items), emotional well-being (6 items), stigma (4 items), social support (3 items), cognition (4 items), communication (3 items), and bodily discomfort (3 items).[30] Each item is graded on a 5-point Likert scale (0 = never; 4 = always), which are then added to generate the respective domain scores. Each domain is scored using a scale of 0 (no problem at all) to 100 (maximum level of a problem). Further, an overall single summary index (the PDQSI) representing the global HRQoL can be created by averaging the 8 subscale scores. The PDQSI is also scored on a scale ranging from 0 to 100, with higher scores indicating worse quality of life.[30,31] Previous research showed moderate to large internal responsiveness for some domains in PDQ-39.[32-34] Findings from the study showed a varying mean MCID for different domains: mobility (–3.2), ADL (–4.4), emotional well-being (–4.2), stigma (–5.6), social support (–11.4), cognition (–1.8), communications (–4.2), and pain (–2.1), and –1.6 for the overall score.[35]

EuroQol 5-Dimensions 5-Levels Questionnaire

The EQ-5D is a generic instrument for measuring health state. It consists of an EQ-5D descriptive system and the EuroQol Visual Analogue Scale (EQ VAS). The descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. In the upgraded EQ-5D 5-Levels (EQ-5D-5L) version, each dimension has 5 levels: a level 1 response represents "no problems" and a level 5 response represents "extreme problems" or "unable to perform." Results from the EQ-5D-5L descriptive system can be converted into a single index score. A score of 0 represents the health state "dead" and 1.0 reflects "perfect health." Negative scores are also possible for those health states that society (not the individual patient) considers to be "worse than dead." The EQ VAS records the respondent's self-rated health on a vertical, visual analogue scale where the end points are labelled 0 ("the worst health you can imagine") and 100 ("the best health you can imagine"). The EQ-5D index and EQ VAS scores can be summarized and analyzed as continuous data.[36] It has been validated in a diverse patient population, including PD, in different countries.[36-38] The internal consistency of the EQ-5D-5L was examined by comparing it to the disease-specific 8-item Parkinson's Disease Questionnaire (PDQ-8), which has similar performance to the PDQ-39 but is shorter and easier to complete.[38] Both the EQ-5D-5L and PDQ-8 index scores were strongly correlated ($r_s = -0.75$), while all of the individual items between the 2 instruments were moderately correlated (correlations ranging from −0.39 to −0.62).[38] Equivalent domains of the EQ-5D-5L and the PDQ-8 (mobility, ADL and self-care, emotional well-being and anxiety) were strongly correlated ($r_s > 0.60$) and the EQ VAS was moderately correlated with both the EQ-5D-5L$_{index}$ and PDQ-8$_{index}$ (r_s of 0.54 and −0.56, respectively).[38] The MCID estimates for the index score in the Canadian population have a summarized mean of 0.056 (SD, 0.011) and

a summarized median of 0.056 (interquartile range of 0.049 to 0.063).[39] Change from baseline in EQ VAS score and index score at week 12 were measured. This outcome was not included in the multiplicity-controlled hierarchical statistical analyses.

Patient Satisfaction

The PGI-I is a patient-rated instrument to evaluate their response to a therapy. The patient's response was rated as the following:[40]

1 = very much improved

2 = much improved

3 = minimally improved

4 = no change

5 = minimally worse

6 = much worse

7 = very much worse.

The end point assessed in CTH-300 was the percentage of patients improved post dosing (e.g., very much improved, much improved, or minimally improved). This was a secondary efficacy end point measured at week 12 in CTH-300 and was included in the hierarchical statistical testing.

Time to Response

Time to response refers to the interval between drug administration and an observed effect. At each study visit, patients were asked about their state (ON or OFF) at 0, 15, 30, 45, 60, and 90 minutes post dose, and were asked to report the time when the study medication was starting to have an effect, if applicable, prompted by the site staff. Time to response at week 12 was a secondary efficacy end point in CTH-300 and was included in the hierarchical statistical testing.

Use of Health Care Services

This outcome was not assessed in CTH-300.

Safety

In CTH-300, TEAEs, SAEs, WDAEs, and AEs of special interest were reported. AEs of special interest were not pre-specified in the study protocol. TEAEs were defined as all AEs that started after the patients received their first dose of the study drug.

Statistical Analysis

The purpose of CTH-300 was to show the superiority of APO SL compared with placebo. No stratification factors were used when patients were randomized. Assuming a treatment difference of 7 points and an SD of 10 points, a sample size of 88 patients (with 44 per group) was needed to provide at least 90% power to detect a statistically significant difference between APO SL and placebo, at a 2-sided significance level of 0.05 using a 2-sample t-test. The rationale for using a treatment difference of 7 points and an associated SD of 10 points in the sample size calculation was not provided. Taking into consideration a 10% dropout rate during the titration phase and a 15% dropout rate during the maintenance phase, the study planned to enrol approximately 126 patients into the titration phase and to randomize approximately 114 patients into the maintenance treatment phase.

No interim analysis was performed. In general, for the efficacy end points analyses, the baseline value of that particular end point was included as a baseline covariate (for continuous end points) or as a stratification factor (for categorical end points). The primary end point for CTH-300 was the change from pre-dose MDS-UPDRS Part III score after 30 minutes at week 12. The difference between treatment groups was estimated using a mixed model repeated measures (MMRM) analysis. The model included the observed change from pre-dose MDS-UPDRS Part III score values after 30 minutes at maintenance treatment visit 1 (MV1) (week 1), MV2 (week 5), MV3 (week 9), and MV4 (week 12) as the response values; the treatment group, visit, and the interaction between the treatment group and visit as fixed factors; and the change from pre-dose MDS-UPDRS Part III score after 30 minutes at the last titration visit as a covariate. The random effects used in the model were not specified in the statistical analysis plan of CTH-300. In case the model did not converge with the unstructured covariance structure, the heterogeneous Toeplitz structure was used instead. In case the model did not converge with the heterogeneous Toeplitz structure, heterogeneous compound symmetry was used instead. The denominator degrees of freedom was computed using the Kenward-Roger method. The LS mean, standard error, and LS mean difference between APO SL and placebo at MV4 along with the 95% CIs were provided. For the analysis of the key secondary end point, the percentage of patients with a patient-rated full ON response within 30 minutes at week 12, estimates were based on logistic regression using a generalized linear mixed model, with the assessment of ON or OFF status at MV1, MV2, MV3, and MV4 as the response values. The model included treatment group, visit (MV1, MV2, MV3, and MV4), the interaction between the treatment group and visit as fixed factors, and the assessment of ON or OFF status at the last titration visit as a covariate. An unstructured covariance structure was used for the repeated measures. In case the model did not converge with the unstructured covariance structure, the heterogeneous Toeplitz structure was used instead. In case the model did not converge with the heterogeneous Toeplitz structure, heterogeneous compound symmetry was used instead. The odds ratios (APO SL versus placebo), 95% CIs for the odds ratios, and P values were provided. All efficacy analyses were conducted in the mITT population (for details, see Analysis Populations, which follows). The time to when study medication was starting to have an effect at week 12 of the maintenance treatment phase was a secondary end point in CTH-300. It was analyzed as a time-to-event end point. The time to effect at week 12 was described using the Kaplan-Meier method to provide an estimate of the median time to effect and corresponding 95% CIs. A Cox proportional hazards model with treatment group as a factor was used to compare APO SL and placebo, and the between-group difference was estimated with a hazard ratio (HR) along with a 95% CI for the HR.

Different approaches were adopted to handle missing data or dropout in CTH-300. The following pre-specified sensitivity analyses were performed for the primary end point:

- completer analysis (conducted using patients completing the study)
- per-protocol analysis (conducted using per-protocol population)
- multiple imputation analyses (with missing-at-random [MAR] assumption or missing-not-at-random assumption [placebo group–based imputation or tipping point–based imputation])
- comparability of the pre-dose values (based on the assumption that the treatment did not influence the pre-dose values during the study)
- last observation carried forward (LOCF) (the missing values were replaced by the previous visit change values at the 30-minute post-dose time point carried forward; an

analysis of covariance (ANCOVA) model, with treatment group as a fixed factor and change from pre-dose in MDS-UPDRS Part III score after 30 minutes at the last titration visit as a covariate, was used to compare the LOCF-imputed values in the mITT population)

- responder analysis based on the MDS-UPDRS Part III scores (response was defined as an improvement of at least 30% decrease in MDS-UPDRS Part III score from the pre-dose value at 15, 30, 45, 60, and 90 minutes. The number and proportion of responders at each time point and the cumulative number and proportion of patients having responded at least once by each time point were tabulated with descriptive statistics at each visit).

In the multiple imputation analyses assuming MAR, the imputation was based on the MAR assumption in that the missing data were assumed to follow the same model as the other patients in their respective treatment arm. Data were structured based on missing data patterns (monotone structure), and the missing values were imputed using the Markov chain Monte Carlo methodology, which assumed a multivariate normal distribution over all of the variables included in the imputation model. The imputed datasets generated with this approach contained only non-missing values. As for the multiple imputation analyses assuming missing not at random, 2 approaches were used to impute the missing values: a placebo group–based imputation where the trajectories of the patients were assumed to follow the placebo group after the discontinuation (thus, the missing values were imputed using a placebo-based imputation), and a tipping point–based imputation where the trajectories of the patients in the APO SL group after withdrawal were assumed to be worse by an amount of delta (thus, the amount of delta was added to each imputed value in the APO SL group, while the multiple imputation analysis using an MAR assumption was used for the placebo group.

For the key secondary efficacy outcome (percentage of patients with a full ON response within 30 minutes post dose), a sensitivity analysis using a Cochran-Mantel-Haenszel test was performed. The test was stratified by the assessment of ON or OFF status within 30 minutes of the last titration visit at which the randomized dose was given and was performed in the mITT population to impute the missing data. For missing data at week 12, the patient was considered to have not reached a full ON response.

Subgroup analyses for selected efficacy end points and AEs performed for predefined factors, such as the baseline MDS-UPDRS Part III score (less than or equal to the median versus above the median), age (< 65 years versus ≥ 65 years), gender, race, and dose level required to achieve a full ON response (10 mg, 15 mg, 20 mg, 25 mg, 30 mg, or 35 mg). Each subgroup was analyzed separately using the same methods as in the primary analysis. For each of the subgroup factors, an MMRM model similar to the primary model was used. Besides the fixed factors and covariate included in the primary model, additional fixed factors for the subgroup variable and the interaction between the treatment group and subgroup variable were included in the model for the subgroup analyses. The influence of each subgroup factor was investigated using the P value for the interaction term calculated with this model. An unstructured covariance matrix was used to model the correlation among repeated measurements and the denominator degrees of freedom were computed using the Kenward-Roger method.

A hierarchical testing approach was used for the analyses of the primary and secondary efficacy end points to control the familywise type I error rate to 5% or less. The end point ranked as first was tested and the difference was declared statistically significant if the nominal P value was less than 0.05. If the difference for the first end point was statistically

significant, the end point ranked as second was tested, and the difference was declared statistically significant if the nominal P value was less than 0.05. The testing continued as long as the previously ranked end point was statistically significant. The sequence of the primary and selected secondary end points tested in the hierarchical test was as follows:

1. Primary end point: Mean change from pre-dose MDS-UPDRS Part III score after 30 minutes at week 12.
2. Key secondary end point: Percentage of patients with a patient-rated full ON response within 30 minutes at week 12.
3. Percentage of patients with a patient-rated full ON response within 30 minutes, the duration of which, from time when study medication begins to have an effect until an OFF (if applicable) response, lasts for at least 30 minutes at week 12.
4. PGI-I: The percentage of patients improved (very much improved, much improved, or minimally improved) at week 12.
5. Clinician Global Impression—Improvement (CGI-I): The percentage of patients improved (very much improved, much improved, or minimally improved) at week 12.
6. Mean change from baseline to week 12 in MDS-UPDRS Part II (motor aspects of experiences of daily living) score.
7. The percentage of instances where a full ON response was achieved 30 minutes after self-administration of the study treatment in the outpatient setting, based on the home dosing diary entries during the 2 days prior to week 12.
8. Mean change from baseline to week 12 in PDQ-39 summary index score.
9. Mean change from pre-dose MDS-UPDRS Part III score at 15 minutes at week 12.
10. Time (in minutes) to when study medication is starting to have an effect at week 12.

Analysis Populations

The intention-to-treatment population consisted of all randomized patients.

The mITT was defined as all patients who were randomized and received at least 1 post-randomization dose of the study drug. The mITT population was used for the efficacy analysis. Patients were grouped based on the assigned treatment.

The per-protocol population was defined as all mITT patients who completed the study with no major protocol deviation.

The safety population included all patients who enrolled and received at least 1 dose of APO SL during the dose titration phase. It was used for the analysis of the safety end points from the dose titration phase and for the pooled data from the dose titration phase and maintenance treatment phase.

The maintenance phase safety population (MPSP) included all patients who received at least 1 dose of the study drug (APO SL or placebo) during the maintenance treatment phase. This population was used for the analysis of the safety end points from the maintenance treatment phase. The patients were grouped according to the medication actually received during the maintenance phase.

The mITT population and MPSP had the same number of patients included; however, based on the definitions of these 2 populations, they did not necessarily include the same patients.

Results

Patient Disposition

A total of 214 patients were screened. Among them, 141 (65.9%) were enrolled into the dose titration phase. The main reasons for screen failure were "eligibility not met" (64.1%) and "consent withdrawal" (19.2%). All 141 patients who entered the dose titration phase received at least 1 dose of open-label APO SL and were therefore included in the safety population. There were 32 (22.7%) patients discontinued during the dose titration phase prior to randomization. The numbers of patients discontinued by highest APO SL dose received in this phase were [redacted] in the 10 mg group, [redacted] in the 15 mg group, [redacted] in the 20 mg group, [redacted] in the 25 mg group, [redacted] in the 30 mg group, and [redacted] in the 35 mg group. AEs (8.5%), lack of efficacy (7.8%), and consent withdrawal (5.7%) were the main reasons for early discontinuation. Among the 11 patients who discontinued the dose titration phase due to lack of efficacy, [redacted] had been titrated to 35 mg and [redacted] had been titrated to 30 mg and were unable to turn ON at any dose. The reason for withdrawal for the 1 patient who did not reach the highest permitted dose of 35 mg was not provided.

In total, 109 patients completed the dose titration phase and were randomized to receive APO SL or placebo in the dose maintenance treatment phase. Eighty patients completed the treatment, 34 (63.0%) in the APO SL group and 46 (83.6%) in the placebo group. AEs (27.8% for APO SL, 9.1% for placebo) were the main reason for treatment discontinuation.

Details of patient disposition are presented in Table 7.

Table 7: Patient Disposition (All Available Populations)

Patient disposition	CTH-300	
	APO SL	Placebo
Screened, N	214	
Dose titration phase		
Enrolled in dose titration phase and received ≥ 1 dose of APO, N	141	
Discontinued during dose titration, n (%)	32 (22.7)	
Adverse events	12 (8.5)	
Lack of efficacy	11 (7.8)	
Patient withdrew consent	8 (5.7)	
Lost to follow-up	1 (0.7)	
Maintenance treatment phase		
Randomized (enrolled in maintenance treatment phase), n	54	55
Patients completed study, n (%)	34 (63.0)	46 (83.6)
Discontinued during maintenance treatment, n (%)	20 (37.0)	9 (16.4)
Adverse events	15 (27.8)	5 (9.1)
Lack of efficacy	0	1 (1.8)
Patient withdrew consent	4 (7.4)	3 (5.5)
Lost to follow-up	0	0
Death	1 (1.9)	0
ITT, n (%)	54 (100)	55 (100)

Patient disposition	CTH-300	
	APO SL	Placebo
mITT, n (%)	54 (100)	55 (100)
PP, n (%)	31 (57.4)	46 (83.6)
Safety population, n (%)	141 (100)	
MPSP, n (%)	54 (100)	55 (100)
Completer population, n (%)	34 (63.0)	46 (83.6)

APO = apomorphine hydrochloride; ITT = intension to treat; mITT = modified intention to treat; MPSP = maintenance phase safety population; PP = per protocol; SL = sublingual.

Source: CTH-300 Clinical Study Report.[15]

Exposure to Study Treatments

A total of 141 patients were exposed to increasing single doses of APO SL (10 mg to 35 mg) in the dose titration phase. The most common highest doses received were 15 mg and 20 mg ([redacted]% and [redacted]% of patients, respectively) (Table 8). Dose selection was based on both the investigator's and patient's assessment of efficacy and tolerability.

Table 8: Extent of Exposure During Dose Titration Phase (Safety Population)

Number of patients, n (%)	Safety population (N = 141)					
	10 mg	15 mg	20 mg	25 mg	30 mg	35 mg[a]
Exposed to single APO SL dose	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Highest dose received	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

APO = apomorphine hydrochloride; sublingual.

[a] This exceeded the maximum dose indicated in the draft drug product monograph (30 mg).

Source: CTH-300 Clinical Study Report.[15]

All patients in the mITT population (54 on APO SL and 55 on placebo) were assessed at MV1. The proportion of patients reaching each of the other 3 maintenance phase visits differed between treatment groups, with a lower proportion of patients in the APO SL group reaching MV2 (placebo: [redacted] patients, [redacted]%; versus APO SL: [redacted] patients, [redacted]%), MV3 (placebo: [redacted] patients, [redacted]%; versus APO SL: [redacted] patients, [redacted]%) and MV4 (placebo: [redacted] patients, [redacted]%; versus APO SL: [redacted] patients, [redacted]%).

At the beginning of the maintenance treatment phase, 54 patients were randomized to APO SL treatment and [redacted] of them ([redacted]%) were assigned to the highest level of APO SL they received in the dose titration phase, while the other [redacted] were assigned to a dose lower than they had previously been exposed to during titration, as permitted by the protocol. A total of 55 patients were randomized to placebo, and [redacted] of them ([redacted]%) were assigned the highest level of APO SL they received in the dose titration phase, while the other 7 were assigned to a dose lower than they had previously been exposed to during titration, as permitted by the protocol.

The mean treatment duration during the double-blind maintenance treatment phase was shorter for patients in the APO SL group ([redacted]) compared with those in the placebo group ([redacted]). According to the patients' diaries, patients in the placebo group ([redacted]) administered more doses compared with those in the APO SL group ([redacted]). The average number of daily doses was lower in the APO SL group (2.2 doses) compared with placebo (2.5 doses) (Table 9).

Table 9: Extent of Exposure During Maintenance Treatment Phase

Exposure	APO SL (N = 54)	Placebo (N = 55)
Duration of exposure, days, mean (SD)[a]	[redacted]	[redacted]
Total doses administered, n[b]	[redacted]	[redacted]
Average number of daily doses, n, mean (SD)[c]	2.20 (1.01)	2.50 (1.09)
AEs leading to dose reduction, n (%)	[redacted]	[redacted]

AE = adverse event; APO = apomorphine hydrochloride; SD = standard deviation; SL = sublingual.

[a] Calculated as date of last dose received in maintenance phase minus date of first dose received in maintenance phase plus 1.

[b] Indicates the number of doses taken across all patients in which dosing information was available.

[c] Average number of daily doses was calculated as the average number of daily doses per patient during the days in which dosing information was recorded.

Source: CTH-300 Clinical Study Report.[15]

A total of 5 APO SL–treated patients had a total of [redacted] that led to dose reduction in the maintenance treatment phase, and nausea was the reason for [redacted].

Efficacy

Only those efficacy outcomes identified in the review protocol are reported (Table 4). Efficacy results were reported in the mITT population in Study CTH-300. See Appendix 2 for detailed efficacy data.

Note that statistical significance was not achieved for the secondary efficacy end points that were ranked third in the hierarchical testing (e.g., percentage of patients at week 12 with a patient-rated full ON response within 30 minutes post dose that had a duration of at least 30 minutes); therefore, statistical significance cannot be formally claimed for any of the end points ranked after this end point. Such end points included:

- PGI-I assessment at week 12
- mean change from screening to week 12 in MDR-UPDRS Part III score
- percentage of instances where a full ON response was achieved at 30 minutes post dose based on the home dosing diary entries during the 2 days prior to the week 12 visit
- mean change from screening to week 12 in the PDQ-39 summary index score
- time to when the study drug was starting to have an effect at week 12.

Mobility (or Hypomobility) by MDS-UPDRS Part III Scores

The primary end point was the mean change from pre-dose to 30 minutes post dose in the MDS-UPDRS Part III score at week 12 in the mITT population using an MMRM analysis in which the treatment group (APO SL or placebo), visit, and the interaction between the treatment group and visit were included as fixed factors, and the change from pre-dose MDS-UPDRS Part III score after 30 minutes at the last titration visit was included as a covariate. The mean change from pre-dose to 30 minutes post dose MDS-UPDRS Part III score for the APO SL group was statistically significantly greater compared with placebo, and the mean treatment difference (APO SL minus placebo) was −7.6 points (95% CI, −11.5 to −3.7; P = 0.0002) (Table 10). The between-group difference in the change from pre-dose to 30 minutes post dose MDS-UPDRS Part III score at week 12 was greater than the MCID for the Part III score. The clinical expert consulted for this review indicated that the difference was considered clinically relevant.

Results of the sensitivity analyses (e.g., in the completer population or per-protocol population) were similar to those observed in the mITT population. Details of the sensitivity analyses are presented in Appendix 2 (Detailed Outcome Measures).

Results of the pre-specified subgroup analyses of the primary end point were generally consistent with those from the primary analyses. The subgroup analyses demonstrated no treatment by subgroup interaction effect at the 5% significance level for age, race, baseline pre-dose MDS-UPDRS Part III score (greater than median versus less than median), or dose assigned. Details of the subgroup analyses are presented in Appendix 2 (Detailed Outcome Measures). There was no adjustment for multiplicity in the subgroup analyses.

Table 10: Change From Pre-Dose MDS-UPDRS Part III Score Over Time at Week 12 (mITT Population)

Outcome parameter	APO SL (N = 54)	Placebo (N = 55)	LS mean difference (APO SL minus placebo), estimate (95% CI)	P value
Time course, mean (SE)				
Pre-dose score	37.2 (12.16)	42.2 (14.88)	–	–
15 minutes post dose	−6.4 (1.22) n = 34	−3.0 (1.08) n = 46	−3.4 (−6.7 to −0.2)	0.0390
30 minutes post dose[a]	−11.1 (1.46) n = 34	−3.5 (1.29) n = 46	−7.6 (−11.5 to −3.7)	0.0002
45 minutes post dose	−13.5 (1.57) n = 33	−3.6 (1.37) n = 45	−9.9 (−14.1 to −5.8)	< 0.0001
60 minutes post dose	−15.0 (1.65) n = 29	−2.3 (1.40) n = 43	−12.7 (−17.0 to −8.3)	< 0.0001
90 minutes post dose	−10.4 (1.69) n = 30	−1.9 (1.44) n = 43	−8.5 (−13.0 to −4.1)	0.0003

APO = apomorphine hydrochloride; CI = confidence interval; LS = least squares; MDS-UPDRS = Movement Disorders Society Unified Parkinson's Disease Rating Scale; mITT = modified intention to treat; MMRM = mixed model repeated measures; MV = maintenance visit; SE = standard error; SL = sublingual.

[a] This was the primary end point. It was analyzed using an MMRM, which included the treatment group (APO SL or placebo), visit (MV1, MV2, MV3, and MV4) and the interaction between the treatment group and visit as fixed factors. The change from pre-dose MDS-UPDRS Part III score after 30 minutes at the last titration visit at which the randomized dose was given, up through titration visit 6, was used as a covariate in the model. An unstructured covariance matrix was used to model the correlation among repeated measurements and the denominator degrees of freedom were computed using the Kenward-Roger method.

Source: CTH-300 Clinical Study Report.[15]

Assessment of ON and OFF States (Frequency of Patient-Rated ON and OFF Episodes)

The key secondary end point in CTH-300 was the percentage of patients with a patient-rated full ON response within 30 minutes post dose at week 12 in the mITT population. A logistic regression using a generalized linear mixed model was used for estimates. Treatment group, visit, and the interaction between the treatment group and visit were included as fixed factors, and the ON-OFF assessment at the last titration visit was used as a covariate. A statistically significant difference was observed in favour of APO SL versus placebo in the percentage of patients achieving a full ON response within 30 minutes post drug administration at week 12 (predicted response rate: 35% for APO SL versus 16% for placebo; adjusted odds ratio: 2.81; P = 0.0426).

For the secondary end point ranked third in the hierarchical testing (percentage of patients at week 12 with a patient-rated full ON response within 30 minutes post dose that had a duration of at least 30 minutes), statistical significance was not achieved (Table 11).

A sensitivity analysis of the key secondary end point was evaluated using a Cochran-Mantel-Haenszel test in which patients whose data were missing at each visit were considered to have not reached a full ON response within 30 minutes. Results of the sensitivity analysis suggested there was no statistically significant difference between APO SL and placebo in the percentage of patients achieving a full ON response within 30 minutes at week 12 (16.4% for placebo versus 25.9% for APO SL; P = 0.1740).

Table 11: Assessment of ON and OFF States at Week 12 (mITT Population)

Outcome parameter	APO SL (N = 54)	Placebo (N = 55)
Patients with a full ON response within 30 minutes post dose (rank second in the hierarchical testing)[a]		
Yes, n (%)	14 (25.9)	9 (16.4)
No, n (%)	20 (37.0)	37 (67.3)
Missing, n (%)	20 (37.0)	9 (16.4)
Predicted response rate	35%	16%
Adjusted OR (95% CI), P value	2.81 (1.04 to 7.64) P = 0.0426	–
Patients with a full ON response within 30 minutes post dose that had a duration of ≥ 30 minutes (rank third in the hierarchical testing)[a]		
Yes, n (%)	12 (22.2)	8 (14.5)
No, n (%)	22 (40.7)	38 (69.1)
Missing, n (%)	20 (37.0)	9 (16.4)
Predicted response rate	31%	14%
Adjusted OR (95% CI), P value	2.80 (1.00 to 7.84) P = 0.0501	–

APO = apomorphine hydrochloride; CI = confidence interval; mITT = modified intention to treat; MV = maintenance visit; OR = odds ratio; SL = sublingual.

[a] This outcome was analyzed in the mITT population based on logistic regression using a generalized linear mixed model procedure. This analysis used the observed values from MV1, MV2, MV3, and MV4 without any imputation as the response. The model included the treatment group, visit, and the interaction between the treatment group and visit as fixed factors. The assessment of ON or OFF response at the last titration visit was used as a covariate. In the case of missing data, the patient was considered to have not reached a full ON response.

Source: CTH-300 Clinical Study Report.[15]

Symptom Reduction

Daytime sleepiness was assessed using the ESS, where a higher score indicates a higher chance of dozing. There were no meaningful changes from baseline for either group. The between-group difference in the change from baseline for the ESS at week 12 was not reported (Table 12). This end point was not included in the hierarchical testing.

Table 12: Summary of Epworth Sleepiness Scale Total Score (mITT Population)

Outcome parameter	APO SL (N = 54)	Placebo (N = 55)
Change from baseline [a] in ESS summary score		
Baseline, mean (SD)	8.9 (4.16)	9.7 (5.08)
Week 12, mean (SD)	10.2 (4.09) n = 34	9.7 (4.68) n = 46
Change from baseline at week 12, mean (SD)	0.5 (3.22) n = 34	−0.6 (3.90) n = 45
Mean difference (APO minus placebo) (95% CI), P value	NR	–

APO = apomorphine hydrochloride; CI = confidence interval; ESS = Epworth Sleepiness Scale; mITT = modified intention to treat; NR = not reported; SD = standard deviation; SL = sublingual.

[a] "Baseline" refers to the screening visit.

Source: CTH-300 Clinical Study Report.[15]

Health-Related Quality of Life

PD-related HRQoL was assessed using the PDQ-39 in CTH-300. The results were estimated using an MMRM, in which treatment group, visit, and the interaction between the treatment group and visit were included as fixed factors, and the baseline PDQ-39 score from the screening visit was included as a covariate. The change in the PDQ-39 summary index from baseline to week 12 was not statistically significantly different between APO SL and placebo (LS mean difference, 1.98 points; 95% CI, −2.16 to 6.12; P = 0.3447).

The EQ-5D-5L was used to evaluate the patient's general well-being. There were no clinically meaningful differences between APO SL and placebo on the change from baseline for the EQ VAS score and EQ-5D index score at week 12.

Details of the HRQoL assessment are presented in Table 13.

Table 13: Health-Related Quality of Life Assessment at Week 12 (mITT Population)

Outcome parameter	APO SL (N = 54)	Placebo (N = 55)
Change from baseline in PDQ-39 summary index[a]		
Baseline, mean (SD)	24.34 (13.57)	28.30 (16.21)
Change from baseline at week 12, LS mean (SE)	0.31 (1.54), n = 32	−1.67 (1.39), n = 45
LS mean difference (APO SL minus placebo) (95% CI), P value	1.98 (−2.16 to 6.12), P = 0.3447	–
EQ VAS score		
Baseline, mean (SD)	68.4 (18.46)	68.3 (18.83)
Change from baseline at week 12, LS mean (SD)	−3.8 (17.69), n = 34	0.0 (26.03), n = 44
Mean difference (APO SL minus placebo) (95% CI), P value	NR	–
EQ-5D index score		
Baseline, mean (SD)	0.65 (0.19)	0.60 (0.24)
Change from baseline at week 12, LS mean (SD)	−0.03 (0.14), n = 34	−0.00 (0.23), n = 45

Outcome parameter	APO SL (N = 54)	Placebo (N = 55)
Mean difference (APO SL minus placebo) (95% CI), P value	NR	–

APO = apomorphine hydrochloride; CI = confidence interval; EQ-5D = EuroQol 5-Dimensions questionnaire; LS = least squares; mITT = modified intention to treat; MMRM = mixed model repeated measures; MV = maintenance visit; NR = not reported; PDQ-39 = Parkinson's Disease Questionnaire 39; SD = standard deviation; SE = standard error; SL = sublingual.

[a] Statistics were from an MMRM analysis that included the observed PDQ-39 change from baseline values at MV1, MV2, MV3, and MV4 as the response values. The model included treatment group, visit (MV1, MV2, MV3, and MV4), and the interaction between the treatment group and visit as fixed factors, and the PDQ-39 score from screening visit as a covariate. An unstructured covariance matrix was used to model the correlation among repeated measurements and the denominator degrees of freedom were computed using the Kenward-Roger method.

Source: CTH-300 Clinical Study Report.[15]

Patient Satisfaction

The PGI-I is a patient-rated scale to assess the overall improvement from a treatment. The percentage of patients who felt their condition had improved (including "very much improved," "much improved," or "minimally improved") from baseline to week 12 was reported. At the end of the maintenance treatment phase, numerically more patients in the APO SL group (20 patients, 37.0%) rated themselves as "improved" compared with the placebo group (11 patients, 20.0%) (Table 14).

Table 14: Assessment PGI-I at Week 12 (mITT Population)

Outcome parameter	APO SL (N = 54)	placebo (N = 55)
Observed improvement status, n (%)		
Improved	20 (37.0)	11 (20.0)
Not improved	[redacted]	[redacted]
Missing[a]	[redacted]	[redacted]
Improvement status, n (%)		
Improved[b]	20 (37.0)	11 (20.0)
Not improved[c]	34 (63.0)	44 (80.0)

APO = apomorphine hydrochloride; mITT = modified intention to treat; PGI-I = Patient Global Impression–Improvement; SL = sublingual.

[a] Missing was counted as not improved in CTH-300.

[b] Improved included a PGI-I assessment of very much improved, much improved, or minimally improved.

[c] Not improved included a PGI-I assessment of no change, minimally worse, much worse, or very much worse.

Source: CTH-300 Clinical Study Report.[15]

Time to Response

Based on a Kaplan-Meier estimate, the median time to response (e.g., interval between drug administration and an observed effect) for APO SL patients at week 12 was 21.2 minutes (95% CI, 15.0 to 27.0), whereas the median time to response for the placebo treatment group was not estimable due to the short duration of the study. The results of a Cox proportional hazards model showed that the HR between treatments for the time to start of effect favoured APO SL (HR 3.4; 95% CI, 1.99 to 5.69; P < 0.0001).

Harms

Only those harms identified in the review protocol are reported (Protocol, Table 4). See Table 15 for detailed harms data.

Adverse Events

During the open-label dose titration phase, 82 of 141 (58.2%) patients experienced at least 1 AE, and the most common AEs reported were gastrointestinal disorders ([redacted]%) and nervous system disorders ([redacted]%).

During the double-blind maintenance treatment phase, AEs were reported in 48 patients (88.9%) in the APO SL group and 25 patients (45.5%) in the placebo group. The majority of the AEs were considered mild to moderate. The proportions of patients reporting severe AEs were 9.3% (5 patients) in the APO SL group and 1.8% (1 patient) in the placebo group. The most common AEs reported with APO SL were gastrointestinal disorders ([redacted]% in the APO SL group versus [redacted]% in the placebo group), followed by nervous system disorders ([redacted]% in the APO SL group versus [redacted]% in the placebo group), respiratory, thoracic, and mediastinal disorders ([redacted]% in the APO SL group versus [redacted]% in the placebo group), general disorders and administration-site conditions ([redacted]% in the APO SL group versus [redacted]% in the placebo group), and psychiatric disorders ([redacted]% in the APO SL group versus [redacted]% in the placebo group).

Serious Adverse Events

One SAE was reported during the dose titration phase, for 1 patient receiving APO SL 15 mg.

During the maintenance treatment phase, a total of 3 patients experienced at least 1 SAE, 2 (3.7%) in the APO SL group (1 fatal cardiac arrest, and 1 congestive heart failure and hypokalemia) and 1 (1.8%) in the placebo group (encephalopathy and acute kidney failure).

Withdrawals Due to Adverse Event

A total of 13 (9.2%) APO SL–treated patients experienced AEs that led to study termination during the dose titration phase.

During the maintenance treatment phase, patients treated with APO SL were more likely to withdraw from treatment due to AEs compared with placebo (27.8% for APO SL versus 7.3% for placebo). Gastrointestinal disorders were the main reasons for treatment discontinuation for patients treated with APO SL ([redacted]%).

Mortality

There was 1 death in the study. The patient was treated with APO SL 15 mg and had a fatal cardiac arrest during the double-blind maintenance treatment phase. The death was considered possibly related to treatment by the investigator.

Notable Harms

In CTH-300, patients in the APO SL group ([redacted]%) were more likely to report gastrointestinal disorders compared with those in the placebo group ([redacted]%). Application-site reactions, such as stomatitis, oral ulcers, and oral irritation were reported by 31.5% of patients in the APO SL group and 7.3% of those in the placebo group. The risks of allergic or sensitivity response to the formulation, daytime sudden onset of sleep, falls and injuries, and hypotension were higher in the APO SL–treated patients compared with placebo. Occurrence of impulsive behaviour and dyskinesia were not reported in the study. Details of AEs of special interest are presented in Table 15.

Table 15: Harm Outcomes

Harms	Safety population (dose titration phase)	Maintenance phase safety population	
	N = 141	APO SL (N = 54)	Placebo (N = 55)
Any TEAEs, n (%)	**82 (58.2)**	**48 (88.9)**	**25 (45.5)**
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]
Nausea	29 (20.6)	15 (27.8)	2 (3.6)
Oral mucosal erythema	6 (4.3)	4 (7.4)	2 (3.6)
Vomiting	6 (4.3)	4 (7.4)	0
Nervous system disorders	[redacted]	[redacted]	[redacted]
Somnolence	16 (11.3)	7 (13.0)	1 (1.8)
Dizziness	16 (11.3)	5 (9.3)	0
Headache	11 (7.8)	3 (5.6)	0
Respiratory, thoracic, and mediastinal disorders	[redacted]	[redacted]	[redacted]
Rhinorrhea	9 (6.4)	4 (7.4)	0
General disorders and administration-site conditions	[redacted]	[redacted]	[redacted]
Fatigue	4 (2.8)	4 (7.4)	0
Psychiatric disorders	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]
Injury, poisoning, and procedural complications	[redacted]	[redacted]	[redacted]
Fall	6 (4.3)	3 (5.6)	1 (1.8)
Lacerations	NR	3 (5.6)	0
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]
Hyperhidrosis	6 (4.3)	3 (5.6)	2 (3.6)
Vascular disorders	[redacted]	[redacted]	[redacted]
Neoplasms benign, malignant, and unspecified	[redacted]	[redacted]	[redacted]
SAEs, n (%)	**4 (2.8)**	**2 (3.7)**	**1 (1.8)**
	One staphylococcal infection from the dose titration phase and 3 from the maintenance phase	One fatal cardiac arrest, 1 congestive heart failure plus hypokalemia	One encephalopathy plus acute kidney failure
WDAEs, n (%)	**13 (9.2)**	**15 (27.8)**	**4 (7.3)**
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]
Respiratory, thoracic, and mediastinal disorders	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]	[redacted]
AEs leading to death	**0**	**1 (1.9)**	**0**
		One fatal cardiac arrest with contributing factor of	

Harms	Safety population (dose titration phase)	Maintenance phase safety population	
	N = 141	APO SL (N = 54)	Placebo (N = 55)
		upper respiratory infection	
AEs of special interest	**50 (30.5)**	**32 (59.3)**	**8 (14.5)**
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]
Stomatitis, oral ulcers, oral irritation	14 (9.9)	17 (31.5)	4 (7.3)
Allergic or sensitivity response to the formulation	2 (1.4)	10 (18.5)	0
Daytime sudden onset of sleep	17 (12.1)	9 (16.7)	1 (1.8)
Falls and injuries	9 (6.4)	5 (9.3)	3 (5.5)
Hypotension, orthostatic hypotension	17 (12.1)	5 (9.3)	0

AE = adverse event; APO = apomorphine hydrochloride; NR = not reported; SAE = serious adverse event; SL = sublingual; WDAE = withdrawal due to adverse event.

Source: CTH-300 Clinical Study Report.[15]

Critical Appraisal

The included study was a phase III, randomized, double-blind, placebo-controlled trial. Appropriate methods of randomization, blinding, and allocation concealment were reported. However, patients were not stratified at randomization. Patients and caregivers were trained in drug administration, identification of ON-OFF status, and keeping records in the patient diaries, which can help minimize bias. In general, patients' baseline demographic and disease characteristics were similar between treatment groups; however, some differences between the APO SL group and the placebo group were noted. For example, the proportion of male patients was higher in the APO SL group than in the placebo group, and the patients assigned to APO SL therapy had a shorter PD history than those in the placebo group. Because a shorter duration of PD may be related to a less severe condition and better response to the current PD treatment at baseline, these patients may be more likely to achieve treatment goals; therefore, the treatment effect of APO SL could be overestimated. However, the impact on study findings is unlikely to be significant. Even though an appropriate method of blinding was used, it may have been difficult to maintain blinding of treatments due to the obvious change in PD symptoms and potential AEs from treatment, particularly for patients who had received previous apomorphine therapy, such as Apokyn. In addition, it is unknown whether the taste of the 2 films was different. The reporting of patient-rated outcomes, such as HRQoL, symptom reduction, and some of the harm outcomes may have been biased. For example, patients who realized they were receiving APO SL film could more easily report a better treatment response or report an AE compared with those receiving placebo film.

Missing data are a particular concern in the efficacy analyses in this study, as the proportion of missing data was substantial and differential between APO SL and placebo. For example, for the assessment of change in MDS-UPDRS Part III score, the percentage of missing data ranged from 37.0% to [redacted]% in the APO SL group and from 16.4% to [redacted]% in the placebo group at the study end point. Since the reasons for such a large proportion of missing data and non-proportional missing data between the 2 treatment groups were not provided in CTH-300, it makes the results uncertain. The results of the sensitivity analyses for the handling of missing data supported the findings from the primary analysis. A

likelihood-based, mixed-effects model, an MMRM, was employed in the primary efficacy analysis and both fixed and random effects were included in the model. Treatment group, visit, and the interaction between treatment group and visit were fixed factors in the MMRM, while the change in pre-dose MDS-UPDRS Part III score after 30 minutes at the last titration visit was used as a baseline covariate in the model. The rationale for the covariance structure selection was not provided. Other factors, such as the baseline severity of the disease or background oral medications for PD, could be considered in the model. Pre-specified sensitivity analyses were conducted using different forms of imputation, with different assumptions (e.g., multiple imputation analysis assuming MAR or missing not at random) for continuous efficacy outcomes, or using different populations (e.g., completer population, per-protocol population). These sensitivity analyses examined the robustness of the primary analysis using different inputs, and the results were similar to the primary data analysis, implying the validity of the primary efficacy analysis. For the key secondary outcome (percentage of patients with a full ON response within 30 minutes post dose), missing data were considered as not reaching full ON status, which may bias the conclusions conservatively.

Multiplicity-controlled analyses using a hierarchical test procedure for series-ranked primary and secondary efficacy outcomes was used in CTH-300 to control the overall type I error rate at 5%. This is a widely adopted method for avoiding inflation of type I error when testing multiple end points. Statistical testing was conditional on the first test being significant, and the second hypothesis was tested with the same alpha level. Statistical testing for the hypotheses was performed only if the previous null hypothesis in the hierarchy could be rejected. A limited number of outcomes were selected; hence, the hierarchical approach did not take into consideration all outcomes measured in the study, including some of the clinically relevant outcomes, such as HRQoL data (e.g., ESS and EQ-5D). HRQoL was identified by patient groups as important outcomes. In addition, no criteria were stated on how the outcomes that were included in the hierarchy were ranked and there was no rationale provided for the selection of the secondary outcomes that were included in the hierarchy.

A number of predefined subgroup analyses based on various patient baseline characteristics were conducted to examine the consistency of the primary analysis results across subgroup levels; however, none of these subgroups was included as a stratification variable at randomization. Thus, the balance of patients' baseline characteristics was less likely to be maintained between such subgroups, and this could subsequently bias the results. Data interpretation was also challenging due to insufficient power to detect a true difference between treatment groups. Wider 95% CIs for the point estimate of between-group differences in efficacy outcomes were observed in several of these subgroups (Appendix 2), which may be expected, given the lack of power within the subgroup analyses. Multiplicity was not controlled for in the subgroup analyses.

Some of the important clinical outcomes for patients with PD were not measured in the included trial, such as change in cognition and mood.

Several validated assessment tools were used to measure function and symptoms related to PD in the included trial. The MDS-UPDRS is a commonly used instrument in clinical trials as well as in clinical practice. The MDS-UPDRS correlated well with the other commonly used tools for PD patients, such as the Hoehn & Yahr scale, the Clinical Impression of Severity Index for PD, the PDQ-8, and the original UPDRS. Strong internal consistency was found for each part of the MDS-UPDRS. Convergent validity and the test-retest reliability of

the MDS-UPDRS were also determined to be satisfactory. In terms of the disease-specific HRQoL assessment tool, the PDQ-39, its validity has been examined in different settings, making the interpretation more generalizable. The reliability, test-retest reliability, and internal consistency were found to be acceptable. The PDQ-39 correlated well with other scales in assessing physical aspects of health status. Internal and external responsiveness varied among the different PDQ-39 domains. The floor and ceiling effects of the PDQ-39 varied in different PD clinical trials. Reliability, floor and ceiling effects, and the construct validity of the ESS were evaluated in PD patients, and the results were considered acceptable. In general, an assessment of the validity of the outcome measures used in CTH-300 suggested these are valid tools for capturing disease state and treatment effects. All patients received training on drug administration, recognizing ON versus OFF status, and maintaining diaries prior to randomization, to ensure quality of assessment and better record keeping.

External Validity

CTH-300 was a multi-centre trial that enrolled patients from 32 US sites and 1 Canadian site. According to the clinical expert involved in the review, the trial used stringent inclusion criteria for patient recruitment that are less commonly observed in clinical practice; in addition, the study population was younger and more representative of mild to moderate disease compared with what is usually seen in Canadian practice, based on the patients' baseline characteristics. However, the study results are likely generalizable to the Canadian patient population.

The dose of APO SL in CTH-300 was inconsistent with the dose proposed in the product monograph. The maximum dose in the study was 35 mg, which was determined to be effective and a tolerable dose for 20 patients (14.2%) in the study population, while in the product monograph, the maximum dose for APO SL film is 30 mg. The clinical expert consulted for this review indicated that this discrepancy should not have a significant impact on the drug's effect in the study population. The use of concomitant levodopa therapy and the pattern of background drug therapy for PD was consistent with Canadian practice.

An enriched population was used in CTH-300 in that patients who were "responders" (responded well and could tolerate the AEs) during the dose titration period were randomized to 1 of the treatment arms. This implies that the chosen patients were more likely to achieve the treatment goal. Although this approach can be beneficial to patients, the sponsor, and regulatory authorities (by identifying a population with an increased likelihood of response and by enhancing efficiency in drug development or enhancing the possibility of using smaller studies to demonstrate treatment effect), the generalizability of the findings from a study with an enriched design to the general patient population is uncertain. Of the 141 patients who met the inclusion criteria for the study, 109 (77%) were enrolled in the double-blind maintenance treatment phase. According to the FDA guidance for industry on the use of enrichment strategies in clinical trials, although some empiric enrichment strategies can efficiently establish the effectiveness of a drug in a subset of the population, they cannot help physicians prospectively identify patients who will have these measured effects.[41] Prior to being enrolled into CTH-300, the appropriateness of potentially eligible patients being included in the study was determined by an external committee. The purpose of this process was to identify appropriate study participants for the trial, which may limit the generalizability of the study results to all patients with PD. In addition, we are not able to evaluate the subgroup of patients susceptible to AEs since they were screened out during the titration phase.

The treatment duration of CTH-300 was 12 weeks, which may not be sufficient to assess the sustainability of the effect of APO SL and LTS in the study population.

Indirect Evidence

Objectives and Methods for the Summary of Indirect Evidence

The clinical trials included in the primary review for APO SL (Kynmobi) did not provide direct evidence regarding the comparative effectiveness and safety of APO SL relative to other therapies for the proposed indication. The aim of this section is to provide an overview and critical appraisal of the published and unpublished indirect evidence available for the assessment of the effectiveness and harms of APO SL compared with the available therapies for the treatment of acute, intermittent OFF episodes in patients with PD.

One network meta-analysis (NMA) was submitted by the sponsor for evaluation of the comparative effectiveness of APO SL versus APO SC (Movapo).[42] In addition, CDR conducted an independent literature search for published ITCs comparing APO SL with other available therapies for the treatment of acute, intermittent OFF episodes in patients with PD. However, no additional published ITCs were identified.

Description of the ITC

The NMA submitted by the sponsor comprised separate searches for studies with APO SL as a primary comparator and studies with APO SC as a primary comparator. The inclusion and exclusion criteria used for the literature search for studies of APO SL are summarized in Table 16. The inclusion and exclusion criteria used for the literature search for studies of APO SC (not shown) were identical to that of APO SL, apart from the reversal of the roles of APO SL and APO SC.

Table 16: PICOS Criteria for Study Inclusion and Exclusion of Studies of Kynmobi

PICOS criteria	Inclusion	Exclusion
Population	Adult (≥ 18 years) patients with PD who experience intermittent OFF episodes Subgroups: • baseline severity of PD (based on MDS-UPDRS or UPDRS score, OFF states, Hoehn & Yahr scale for staging the severity of PD, and so forth) • baseline oral medications for PD • type of OFF episodes (e.g., wearing OFF, morning OFF, or unpredictable OFF episodes)	• Patients < 18 years • PD patients that do not experience OFF episodes • All other diseases
Interventions	APO SL (Kynmobi) (i.e., APL-130277 formulation of sublingual apomorphine hydrochloride) administered as acute intermittent treatment for OFF episodes, added to 1 or more background oral medications for PD	• Intervention was not administered as an acute intermittent treatment for OFF episodes • Intervention was not titrated to an effective dose prior to study initiation

PICOS criteria	Inclusion	Exclusion
Comparisons	• APO SC (Movapo) administered as an acute intermittent treatment for OFF episodes, added to 1 or more background oral medications for PD • Placebo administered as an on-demand treatment for OFF episodes, added to 1 or more background oral medications for PD	• Intervention was not administered as an acute intermittent treatment for OFF episodes • Intervention was not titrated to an effective dose prior to study initiation • Studies that do not contain comparators of interest
Outcomes	• Mobility (or hypomobility) by validated measure (e.g., MDS-UPDRS motor score, UPDRS motor score, Dyskinesia Rating Scale, hand-tapping test scores, step-seconds test scores) • Improvement by validated measure: CGI-I, PGI-I, PDQ-39 • Duration of ON per episode • HRQoL • Symptom reduction (e.g., tremor, bradykinesia, rigidity, postural instability) • Time to response (interval between administration and declared recovery) • Proportion of doses declared to have aborted the OFF event • Inability to self-administer the study medication • Nonresponse to treatment • Use of health care services (hospitalization, physician office visits, and so forth) • TEAEs, SAEs, mortality, notable harms and harms of special interest (dyskinesia, oral, or injection-site reaction, postural hypotension, impulsive or asocial behaviour, other dopaminergic AEs)	Studies that do not contain any relevant outcomes
Study design	Randomized controlled trials	Studies that were not randomized controlled trials (i.e., reviews, observational or single-arm studies, commentaries)

AE = adverse event; APO = apomorphine hydrochloride; CGI-I = Clinician Global Impression—Improvement; HRQL = health-related quality of life; MDS-UPDRS = Movement Disorder Society Unified Parkinson's Disease Rating Scale; PD = Parkinson disease; PDQ-39 = Parkinson's Disease Questionnaire 39; PGI-I = Patient Global Impression—Improvement; PICOS = population, intervention, comparison, outcomes, and study; SAE = serious adverse event; SC = subcutaneous; SL = sublingual; TEAE = treatment-emergent adverse event; UPDRS = Unified Parkinson's Disease Rating Scale.

Sources: Sponsor-provided network meta-analysis.[42]

Review and Appraisal of ITC

Review of the Sponsor-Provided NMA

Objectives and Rationale for the Sponsor-Provided NMA

The objective of the SLR and subsequent ITC was to evaluate the comparative effectiveness and safety of APO SL compared with APO SC for the treatment of acute, intermittent OFF episodes associated with PD. Conclusions of comparative effectiveness were based primarily on mean differences for measures of hypomobility in patients with PD, including MDS-UPDRS motor scores and UPDRS motor scores. Secondary outcomes included duration of ON status per episode, time to response, and proportion of OFF episodes that responded to treatment.

Methods for the Sponsor-Provided NMA

Study Eligibility and Selection Process

The authors indicated that the SLR and ITC were conducted to adhere to the checklist from the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA). The search criteria were established using the PICOS framework. The authors acknowledged that the PICOS used for the search was not published or registered, but claimed that it was specified a priori. Multiple databases were included in the SLR, including Ovid, MEDLINE, Embase, and the Cochrane Library. Separate searches were conducted on March 6, 2018 and April 6, 2018 for sublingual and subcutaneous apomorphine strategies, respectively. These 2 searches were updated on January 27, 2020 and again on May 20, 2020. Subsequent monthly alerts were performed for each search, with the last monthly alert run on February 1, 2019.

The primary inclusion criteria for studies in the search were adult (≥ 18 years) patients with PD who experience intermittent OFF episodes. Study screening was conducted in 2 stages by 2 reviewers who independently reviewed articles identified through the literature search. Reasons for exclusions were documented throughout. Disagreements between reviewers were resolved through discussion or by a third independent reviewer.

Data Extraction

The data were extracted by 1 reviewer and verified by a second reviewer. Disagreements were resolved through discussion or by a third independent reviewer.

Comparators

The primary comparators for the SLR and subsequent ITC were sublingual and subcutaneous administrations of apomorphine. A placebo intervention was the only other comparator allowed for a study to be included in the SLR.\

Outcomes

The main end points of interest included in the SLR were stated to be:

- mobility (or hypomobility) by validated measure (e.g., MDS-UPDRS motor score, UPDRS motor score, Dyskinesia Rating Scale, hand-tapping test scores, step-seconds test scores)
- improvement by validated measure: CGI-I, PGI-I, PDQ-39
- duration of ON per episode
- HRQoL
- symptom reduction (e.g., tremor, bradykinesia, rigidity, postural instability)
- time to response (interval between administration and declared recovery)
- proportion of doses declared to have aborted the OFF event
- inability to self-administer the study medication
- nonresponse to treatment
- use of health care services (hospitalization, physician office visits, and so forth)

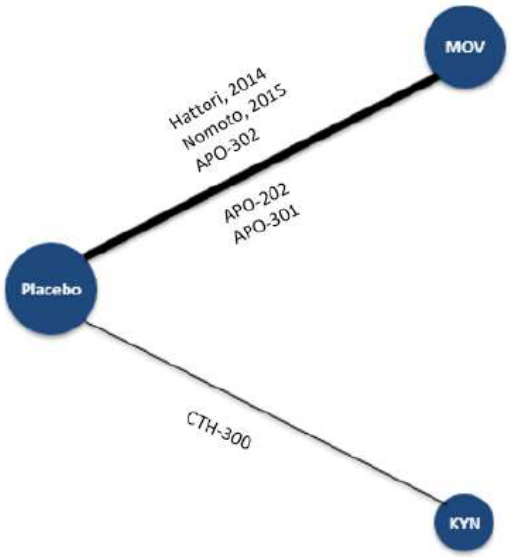
- TEAEs, SAEs, mortality, notable harms and harms of special interest (dyskinesia, oral, or injection-site reaction; postural hypotension; impulsive or asocial behaviour; other dopaminergic AEs).

Quality Assessment of Included Studies

The risk of bias assessment was performed using the Cochrane Risk of Bias Assessment Tool for Randomized Controlled Trials. Reviews were performed in duplicate and disagreements were resolved by discussion or by a third independent reviewer.

Evidence Network

Figure 3: Schematic of the Evidence in the Sponsor-Included NMA



Characteristic	Number
Number of Interventions	3
Number of Studies	6
Total Number of Patients in Network	306
Total Possible Pairwise Comparisons	3
Total Number Pairwise Comparisons With Direct Data	2
Number of Two-arm Studies	6
Number of Multi-arms Studies	0

APO = apomorphine hydrochloride; KYN = Kynmobi; MOV = Movapo; NMA = network meta-analysis.

Sources: Sponsor-provided NMA.[42]

ITC Methods

All analyses used a Bayesian modelling approach using NetMetaXL and WinBUGS (version 1.4.3). Model runs used a burn-in sample of 40,000 iterations with subsequent sampling of 40,000 iterations. The authors did not specify whether multiple chains were used or how convergence was assessed. The prior distributions used for analysis were not explicitly stated, but portions of the submitted report allude to the use of vague priors.

Both fixed-effect and random-effects models were produced for each analysis. The authors' choice a priori was to report results from the fixed-effects model as primary due to the small number of studies included in the network. The model fit for all analyses was assessed using deviance information criterion (DIC).

The primary outcome examined for comparative effectiveness was change in hypomobility assessments measured by MDS-UPDRS and UPDRS motor scores. Hypomobility was assessed among the APO SL studies using the MDS-UPDRS motor score, whereas studies

comparing APO SC utilized the UPDRS motor scores. Due to reports of a high degree of correlation between these 2 measures (97%) and a validated conversion method that recommended the addition of a constant that would not alter estimates of a change from baseline, the results were compared across the study without accounting for the 2 different scales. The timing of measurement after treatment administration also differed by study, where the primary study for APO SL measured MDS-UPDRS motor score at 15, 30, 45, 60, and 90 minutes post exposure, and studies of APO SC had measures of UPDRS available at 20, 60, and 90 minutes post exposure. For the primary outcome comparison, the authors chose to compare the 30-minute measurement point from the APO SL study with the 20-minute measurement point from the APO SC studies. As secondary comparisons, the authors also separately compared measurements at 60 and 90 minutes. The primary comparison also exclusively used the MDS-UPDRS motor score measures from the APO SL studies taken during the final study visit at 12 weeks. Since the APO SC studies were generally of shorter duration, the authors replicated the analysis using 3 early study visits from the APO SL study as a sensitivity analysis.

Another secondary outcome that was compared was the mean duration of ON response following treatment administration. This outcome was not directly measured or reported by either the APO SL or APO SC studies and, so, was derived by other measures from each study. One study for each treatment was deemed to have sufficient information to derive the duration of ON outcome, those being CTH-300 for APO SL and APO-202 for APO SC. For CTH-300, ON status was evaluated based both on patient and clinician reports at discrete time points relative to treatment administration during study visits: baseline and 15, 30, 45, 60, and 90 minutes after exposure. The duration of ON response was estimated for each visit for each patient by identifying the 2 time points when a patient switched from OFF to ON status and again from ON to OFF. The midpoint between the 2 identified points was used as the start and stop time for the duration of ON. All patients were initially OFF at baseline, thus, the switch from OFF to ON status was observed for all patients. For patients who were ON at the final observation point (90 minutes), a time of 105 minutes post exposure was used as the end of the ON episode. The patient-reported duration of ON was ultimately used for comparison, since it was considered most comparable to APO-202, which also relied on patient-reported data. For APO-202, the mean duration of ON was calculated by dividing the study-reported mean reduction in OFF hours per day by the mean number of treated episodes per day. Both of these means were based on patient-reported diaries of treatment episodes. The authors did not specify how the variance components for this measure were calculated.

Heterogeneity was assessed across the studies through comparison of the baseline demographic and clinical measures, including gender, age, race, time since diagnosis, baseline UPDRS or MDS-UPDRS motor score, and levodopa daily dose. If heterogeneity was deemed to be a concern, sensitivity analyses were conducted, when possible.

Results of ITC

Summary of Included Studies

For the APO SL intervention search, 2 RCTs were identified for inclusion in the ITC, those being CTH-201 and CTH-300. For the APO SC intervention search, 6 RCTs were identified for inclusion in the ITC. Each study compared the treatment of interest with placebo, and there were no direct comparisons made between APO SL and APO SC. For all included studies, treatment was titrated to an effective dose. Each study titrated on the study drug except for 1 study, APO-202, where patients randomized to placebo were titrated on

placebo. All APO SL studies removed patients who did not respond to any titrated treatment doses prior to randomization. Two APO SC studies, Hattori[43] and Nomoto,[44] similarly removed nonresponders from the study. All other studies of APO SC either did not report on treatment for nonresponders or did not remove them from the study. In CTH-300, anti-PD medication was withheld overnight prior to the study visit to assess study medications during morning OFF periods, whereas stable doses of concomitant medications were permitted for CTH-201. Standard PD medication was withheld overnight prior to assessment for APO-202, while its use was permitted for APO-301 and APO-302. The handling of standard PD medications was not reported for 3 studies of APO SC. Length of follow-up varied considerably between the studies, with the 2 APO SL studies having follow-ups of 3 days and 12 weeks and the APO SC studies varying in length from 2 days to 12 weeks.

The authors reported that the overall risk of bias of the included RCTs was low. Many of the studies did not provide enough details on randomization or allocation concealment for these factors to be assessed. Two studies of APO SC, APO-301 and APO-302, had an unclear risk of bias due to potential loss of blinding since all recruited patients had previous long-term exposure to apomorphine. Two studies, CTH-300 and Ostergaard,[45] had some risk of bias due to incomplete outcomes, primarily due to dropout. One study, APO-301, was at risk of bias due to selective reporting since results were not formally published.

Table 17 presents summary statistics for the key baseline characteristics of the studies included in the comparison. The authors noted differences in patient baseline characteristics across the included studies for all of the variables included for comparison, but concluded that the observed differences were not likely to impact the comparability of the trials. In particular, variation in level of daily levodopa dose was considered to be a result of differences in treatment practices across time and jurisdictions and not likely related to disease severity. Patients from studies APO-301 and APO-302 all had previous exposure to apomorphine, which was deemed a limitation for including these studies in the comparison of safety outcomes, but not a limitation for comparisons of efficacy.

Table 17: Baseline Patient Characteristics of Included Studies

Study	Treatment	Gender (% male)	Mean age	Race (% White)	Mean time since diagnosis (years)	Mean baseline MDS-UPSDRS Part III OFF score	Mean ON stage (modified Hoehn & Yahr stage)	Mean daily levodopa dose (mg)	Prior exposure to APO (%)
Kynmobi versus placebo									
CTH-300	APO SL	68.5	62.9	92.6	8.7	43.2[a]	2.2	1,058.7	1.9
	PL	56.4	62.5	92.7	9.3	43.1[a]	2.2	1,007.7	3.6
CTH-201	APO SL and PL	65.0	63.7	92.5	8.3	NR	NR	620.5	NR
APO SC versus placebo									
Hattori (2014)[43]	APO SC and PL	58.1	61.6	NR	NR	41.8	2.1	491.9	0.0
Nomoto (2015)[44]	APO SC	40.0	57.7	NR	9.1	47.2	2.5	520.0	0.0
	PL	16.7	58.8	NR	11.6	41.3	2.8	658.3	0.0
APO-302	APO SC	71.4	64.8	100.0	13.0	NR	NR	NR	100.0
	PL	74.1	66.5	92.6	16.0	NR	NR	NR	100.0
APO-202	APO	60.0	66.0	95.0	9.2	39.7	NR	776.0	0.0
	PL	89.0	62.0	88.9	12.3	36.3	NR	819.0	0.0
Ostergaard (1995)[45]	APO SC and PL	45.5	59.3	NR	9.8	NR	NR	NR	31.8
APO-301	APO SC and PL	70.6	61.7	100.0	13.7	41.3	NR	NR	100.0

APO = apomorphine hydrocholoride; MDS-UPDRS = Movement Disorders Society Unified Parkinson's Disease Rating Scale; NR = not reported; PL = placebo; SC = subcutaneous; SL = sublingual.

[a] CTH-300 and CTH-201 reported baseline MDS-UPDRS Part III scores. Using a published conversion method, the authors reported the MDS-UPDRS Part III equivalent scores as 36.2 and 36.1 in CTH-300 and CTH-201, respectively.

Source: Sponsor-submitted network meta-analysis.[42]

Results

Efficacy

The authors evaluated the clinical efficacy of APO SL and APO SC relative to differences in UPDRS and MDS-UPDRS motor scores at 20 or 30 minutes, 60 minutes, and 90 minutes from baseline and duration of ON per treatment using a formal NMA approach. Other outcomes were evaluated but were ultimately excluded from formal comparison for various reasons related to inconsistencies in the reported outcomes across studies and sparsity in both the data and the network. These other outcomes included time to response, proportion of patients who turned ON after treatment, CGI-I, PGI-I, PDQ-39, HRQoL, symptom reduction, proportion of patients unable to self-administer, proportion of nonresponse to treatment, and use of health care services. Only 1 APO SL study, CTH-300, was used for each efficacy outcome. Five of the 6 APO SC studies contributed to the primary outcome of mean difference in UPDRS or MDS-UPDRS motor score at 20 or 30 minutes: Hattori, [43] Nomoto,[44] APO-202, APO-301, and APO-302. One APO SC study contributed to each of the comparisons for mean difference in UPDRS or MDS-UPDRS motor score at 60 and 90 minutes and the duration of ON outcome, those being APO-301, APO-302, and APO-202, respectively.

The results of the NMA comparison for the 4 assessed outcomes are presented in Table 18. For the primary outcome of differences in UPDRS or MDS-UPDRS motor score at 20 or 30 minutes, the analysis showed a larger decrease in mean motor score for patients on APO SC compared with those on APO SL, with APO SL patients decreasing 12.40 points less on average (95% CrI, 7.63 to 17.17). At 60 minutes from baseline, the results did not favour either treatment (mean difference, −0.52; 95% CrI, −8.01 to 6.98). At 90 minutes from baseline, a mean difference was estimated that favoured APO SL (mean difference, −8.21; 95% CrI, −15.02 to −1.38). The duration of ON per treated episode was estimated to increase by 4.38 minutes for APO SL compared with APO SC, but this difference did not clearly favour APO SL based on the CrI (95% CrI, −7.45 to 16.18). The reported DIC for each of these results showed little difference in fit between the fixed-effects and random-effects models (UPDRS or MDS-UPDRS motor score at 20 or 30 minutes: 33.9 versus 34.1; 60 minutes: 11.51 versus 11.51; 90 minutes: 11.24 versus 11.27; duration of ON: 9.41 versus 9.43).

Table 18: Efficacy Outcome Measures for APO SL Compared With APO SC Assessed Using an NMA

Outcome	Mean difference (95% CrI)
UPDRS or MDS-UPDRS motor score[a]	
20 or 30 minutes[b]	12.40 (7.63 to 17.17)
60 minutes	−0.52 (−8.01 to 6.98)
90 minutes	−8.21 (−15.02 to −1.38)
Duration of ON[c]	
Patient-reported (in minutes)	4.38 (−7.45 to 16.18)

APO = apomorphine hydrocholoride; CrI = credible interval; MDS-UPDRS = Movement Disorders Society Unified Parkinson's Disease Rating Scale; NMA = network meta-analysis; SC = subcutaneous; SL = sublingual; UPDRS = Unified Parkinson's Disease Rating Scale.

Note: All estimated mean differences are for the mean for APO SL patients minus the mean for APO SC patients. Estimates are based on a fixed-effects model using a Bayesian approach.

[a] MDS-UPDRS motor score was used for APO SL studies, whereas the UPDRS motor score was used for APO SC studies.

[b] The motor scores measured at 20 minutes for patients on APO SC were compared with scores measured at 30 minutes for APO SL patients.

[c] Duration of ON was estimated based on a ratio of the estimated mean reduction in OFF hours per day to the estimated mean number of treatment episodes per day for the APO SC study and approximated for the APO SL study based on monitoring of ON status at discrete points post exposure.

Source: Sponsor-submitted NMA.[42]

Safety

The authors evaluated the safety outcomes reported by the 8 included studies, including AEs, TEAEs, and SAEs. Ultimately, the authors concluded that the safety results could not be formally compared between APO SL and APO SC, primarily due to study heterogeneity. Two key sources of heterogeneity in particular were noted by the authors: inconsistent prior exposure to apomorphine, and variation in study duration. Two studies consisted of patients recruited from a previous study where all patients received long-term exposure to apomorphine. The authors argued that patients who consented to the additional studies would be less likely to experience AEs; hence, these studies were excluded from the assessment of safety. The remaining studies that reported on safety outcomes varied considerably in their trial duration. The authors anticipated that trials of shorter duration would be less likely to observe AEs than trials of longer duration, and therefore concluded that the safety outcomes could not be formally compared in an NMA. Summaries of safety outcomes are presented for descriptive purposes in Table 19. The rate of TEAEs was fairly high for all trials except CTH-201. The difference in the rate of TEAEs between the 2 APO SL studies supports the concern for the differing trial durations. The difference in the rate of TEAEs as it relates to trial duration was less pronounced between the 2 APO SC studies. The rate of SAEs was relatively low among trials that reported on this outcome, but the precision of these estimated rates are limited by the small sample sizes of the trials.

Table 19: Descriptive Comparison of TEAEs and SAEs by Study and Intervention

Study	Trial duration	Treatment	Sample size	TEAEs (%)	SAEs (%)
APO SL versus placebo					
CTH-300	12 weeks	APO SL	54	88.9	3.7
		Placebo	55	45.5	1.8
CTH-201	3 days	APO SL	40	32.5	0.0
		Placebo	40	15.0	0.0
APO SC versus placebo					
Nomoto (2015)[44]	1 day	APO SC	10	70.0	NR
		Placebo	6	83.3	NR
APO-202	4 weeks	APO SC	20	85.0	0.0
		Placebo	9	89.0	11.1

APO = apomorphine hydrocholoride; NR = not reported; SAE = serious adverse event; SC = subcutaneous; SL = sublingual; TEAE = treatment-emergent adverse event.

Source: Sponsor-submitted network meta-analysis.[42]

Critical Appraisal of the ITC

In the sponsor-provided NMA, the analyses were based on an SLR to identify all relevant RCTs that compared either sublingual or subcutaneous administrations of apomorphine. The scope of the search as described seemed sufficiently broad, and the screening of potential studies for inclusion was sufficiently rigorous. The risk of bias for all individual studies was assessed using the Cochrane Risk of Bias tool, and all studies generally had a low risk of bias, according to the authors. Although potential concerns in study design were noted for inadequate reporting of randomization and allocation concealment as well as risks of unblinding for some studies, no sensitivity analyses were performed to evaluate any potential influence of these risks. In addition, high levels of missing data were noted as introducing unclear bias for 2 studies, including CTH-300. This report has already commented on the uncertainty of these results due to the amount of missing data in this study. Sensitivity analyses were conducted to evaluate the impact of missing data on study findings. The results of the sensitivity analyses on the handling of missing data supported the findings from the primary analysis. The search identified 8 studies in total, 6 of which had fewer than 36 patients in each intervention arm. Thus, the comparisons were based on a small network of trials with limited sample size, especially considering that all but 1 of the formal comparisons were based on a single study for each comparator and no studies directly compared the 2 interventions of interest. Inconsistencies were found in the reported study design and the characteristics for some studies, both within different areas of the report as well as relative to the article referenced for the study. One study, Hattori,[43] was not included in the author's assessment of safety outcomes since this study did not report on the rate of AEs among the placebo arm. Also, Ostergaard[45] was excluded from all comparisons since several efficacy outcomes and the AEs reported were not considered reliable.

Heterogeneity was assessed by comparing baseline demographic and clinical measures across studies and was generally not considered by the authors to be a concern, with the exception of variations in length of follow-up across studies and prior exposure to apomorphine. The variation in the length of time until study follow-up was primarily considered to be a limitation for evaluating safety, due to some AEs being less likely to be captured in a study of shorter duration. Since the APO SC studies tended to be of shorter

duration compared with the other studies that reported on safety outcomes, this limitation likely biased the comparison of safety outcomes conservatively for APO SL. In addition, 2 studies of APO SC consisted of patients recruited from a previous study in which all patients experienced long-term exposure to APO SC, whereas all patients from the other studies had relatively little or no previous exposure to apomorphine. This was primarily considered to be a limitation for the comparison of safety outcomes, since patients in the 3 studies would likely be patients who had experienced fewer AEs in the previous study. However, this could also impact the comparison of efficacy outcomes, since the placebo effect could be underestimated in each of these studies due to the potential unblinding of patients in the placebo groups who had previously had long-term exposure to the study drug. Since each of these studies compared APO SC with placebo, this limitation would likely bias conclusions conservatively for APO SL.

Based on the assessment of heterogeneity, the authors specified 2 sensitivity analyses to evaluate the impact of heterogeneity on study conclusions. The first sensitivity analysis evaluated the influence of varying study duration by comparing the motor score measures from the APO SC studies to MDS-UPDRS motor scores taken at earlier study visits in the APO SL study. For the comparison of UPDRS or MDS-UPDRS motor score at 20 or 30 minutes, 60 minutes, and 90 minutes, results based on different study visits were reasonably consistent with the primary result which was based on the final study visit at 12 weeks. The second sensitivity analysis proposed to remove studies APO-301 and APO-302 from the primary analysis of the UPDRS or MDS-UPDRS motor score at 20 minutes or 30 minutes due to these studies recruiting patients with previous exposure to APO SC. This sensitivity analysis could not be conducted for any other study since all other outcomes were based on a single study comparison. Results of this sensitivity analysis were similar to the primary analysis.

There were several other sources of heterogeneity that were not considered of concern to the authors. Two studies of APO SC, Hattori[43] and Nomoto[44], were conducted in Japan and likely had a different distribution of race compared with the other studies, which consisted largely of patients who were White. In general, levels of impairment due to PD as well as treatment practices have been shown to be highly variable across genetic and regional factors. The exact impact that this heterogeneity may have on study conclusions is unknown. However, the differences in race across trials were less likely to have a significant impact on the comparability of the included trials for the purpose of the ITC, given that the clearance of APO SL does not appear to be influenced by race, according to the product monograph for Kynmobi.[14] Other variables also indicated differences in patient populations across studies that relate to disease severity and treatment. Although each study consisted of patients of similar age and baseline measures of hypomobility, patients from the APO SC studies were observed to have had a longer time since diagnosis and lower levels of daily levodopa dose. These factors may have made patients in the APO SC studies more likely to respond to treatment with APO SC; thus, these studies may have overestimated the treatment effect for APO SC. Hence, this limitation could bias conclusions conservatively for APO SL. The shorter durations of disease for APO SL patients may also imply that a larger portion of these patients were DA naive. Since DAs have many associated side effects in common with apomorphine, this difference may have conservatively impacted comparisons of safety outcomes for APO SL, since patients who were naive to DAs could be more sensitive to these associated AEs. Another limitation of the safety assessment was that the APO SC studies excluded patients with orthostatic hypotension since APO SC was contraindicated for such patients. This further biases the safety comparison for APO SL. Moreover, patients, in general, are expected to be more

willing to initiate a sublingual therapy compared with a subcutaneous injection. Thus, the comparison between APO SL and APO SC will be limited due to the appeal of APO SL to a wider patient population.

The general methodological approach used for the NMA was deemed appropriate. The use of a Bayesian framework using fixed effects as the primary model seems reasonable, given the small number of identified studies. Random-effects results were also provided for each analysis and were generally consistent with the fixed-effects results. One important omission in the submitted report was a description of the approach used to assess convergence or whether multiple chains were implemented for each model. Without these specifications, there is no assurance that the estimates presented are from a converged model or that the estimates represent unique solutions to the model. Furthermore, the prior distributions used in the analyses were not specified, nor were any sensitivity analyses reported for evaluating the sensitivity of results to the specified priors.

Results of an ITC analysis comparing APO SL with APO SC suggest that the former was associated with a smaller improvement and had a less robust effect on hypomobility between 20 and 30 minutes after drug administration, but a potentially superior effect after 90 minutes compared with the latter. The secondary comparisons did not provide evidence for a differing effect between the 2 treatments for change in UPDRS or MDS-UPDRS at 60 minutes or for duration of ON, but APO SL was estimated to have a larger effect for change in UPDRS or MDS-UPDRS at 90 minutes. For UPDRS and MDS-UPDRS motor scores, a clinically meaningful decrease in these scores has been reported to be 3.25 points. The lower bound of the 95% CrI for the outcome measured at 20 or 30 minutes was 7.63 points, suggesting that the improved effect from APO SC is clinically relevant at this time point. At 60 minutes, the bounds of the 95% CrI were −8.01 and 6.98 points, which means a clinically meaningful benefit for either APO SL or APO SC cannot be ruled out based on this comparison. At 90 minutes, the point estimate of −8.21 points exceeded the MCID threshold, but the value of −1.38 points for the upper bound of the 95% CrI does not definitively support the conclusion that APO SL has a clinical meaningful benefit compared with APO SC. For the duration of ON outcome, the 95% CrI suggests that APO SL, at worst, results in a reduction of 7.45 minutes per ON episode, but the benefit could be as large as 16.18 minutes. No clinical criterion was provided for a meaningful effect for this outcome, so no further clinical interpretation of these results can be done. Finally, the presence of too many sources of heterogeneity precluded a formal comparison of safety outcomes for these 2 treatments. Descriptive comparisons showed similar, high rates of TEAEs for APO SL and APO SC, but the limitations of this comparison likely bias the comparison conservatively for APO SL.

There were several limitations in the outcomes used for the efficacy comparisons. First, the APO SL and APO SC studies used 2 different scales for measuring hypomobility motor scores: the MDS-UPDRS and the UPDRS. Though these 2 scales are highly correlated, this adds uncertainty to the comparison of motor scores across studies. The difference in the scales was not accounted for in the study due to the use of a published conversion approach wherein a constant value is subtracted from the MDS-UPDRS motor score, which would not impact the comparison of a change in motor score from baseline.[46] However, an alternative conversion approach is also widely used that uses different conversions across groups defined by Hoehn & Yahr stage.[47] This conversion would impact a comparison relative to baseline and thus could have been used in a sensitivity analysis to assess how results might be altered by the different conversion approaches. Second, the timing of the UPDRS or MDS-UPDRS measures to determine the primary outcome differed among the

studies, with the CTH-300 study measuring the change in hypomobility at 30 minutes and the APO SC studies measuring it at 20 minutes. The authors chose these time points since the 30-minute measure in CTH-300 was considered the best time point for representing the peak plasma concentration for APO SL, while the 20-minute measure used in the APO SC studies was closest in proximity. Thus, the conclusions of the NMA are limited by the lack of a common time point for the peak concentration of APO SL. Third, the comparison of the duration of ON outcome was limited because this outcome was not directly reported by any of the studies; rather, it was derived based on the other data presented in the studies. For the APO SC study used for this outcome, duration of ON was calculated based on a ratio of the mean reduction in OFF time to the mean number of injections per day, which was estimated from the study sample of 20 patients exposed to APO SC. While this approach is intuitive, such an approach is known to provide a biased estimate for the true ratio, particularly for finite sample sizes.[48] The authors also did not specify how the variance of this ratio was calculated, which has implications on the level of bias of the estimated effect as well as on the overall inference for this comparison, since the variance estimates may also be biased. Based on the theoretical bias of this estimate and that the reduction in OFF time and number of injections will likely be positively correlated, the reported estimate likely overestimates the true mean of the duration of ON for the sample. Thus, this limitation likely biases conclusions conservatively for APO SL. For the APO SL study, the calculation of the duration of ON inferred the starting and stopping points of the ON response based on discrete observations of patients' ON or OFF status post-treatment. This approach adds uncertainty to this comparison, but whether this approach may have biased the study conclusions is unclear. Another key difference in the data used for this outcome between the APO SC and APO SL studies is that the APO SC study collected this data from patient diaries recording episode responses, the majority of which would have taken place outside of a clinical setting, whereas the APO SL study collected the data during study visits under clinician observation. Thus, the derivation of duration of ON being based on 2 different settings for patient-reported measures also adds to the uncertainty of this comparison.

Finally, a limitation of the reported NMA is the key differences in the placebo arms used as a comparator in each of the studies. Since the ITC of APO SL and APO SC is anchored by the placebo intervention, the estimated difference between the 2 treatments relies on the assumption that the true placebo effect in each study is the same, i.e., the transitivity assumption. However, across the APO SL and APO SC studies, the placebo arm varies in the administration approach used, where the APO SL studies used a sublingually administered placebo and the APO SC studies used a subcutaneous injection of a placebo. Studies have shown that the magnitude of the placebo effect can depend on the administration approach, particularly for subjective measures such as the outcomes in the current NMA, which rely on clinician and patient evaluation.[49,50] If the placebo effect does differ across the studies, the transitivity assumption of the NMA would be violated and the resulting estimates would be biased. The difference in placebo effect was noted by the authors as a limitation of the comparison of safety outcomes, but this limitation would also apply to the efficacy outcomes. Studies suggest that a subcutaneous injection would likely have a more robust placebo effect compared with a sublingual placebo for measures of efficacy[49] which, if true, would bias the comparison anti-conservatively for APO SL. However, a larger subcutaneous placebo effect was not consistently observed among the APO SC studies compared with the sublingual placebo effect in CTH-300. In particular, for the primary outcome of UPDRS score at 20 minutes or MDS-UPDRS score at 30 minutes, only 1 APO SC study estimated a larger placebo effect, whereas 3 studies estimated a similar placebo effect (within 2 points), and 1 study estimated a smaller, near-zero placebo

effect. Other previously mentioned factors may explain why the subcutaneous placebo effect was underestimated in the APO SC studies, such as the placebo group being titrated on placebo, patients having previous long-term exposure to the study drug, and other sources of study heterogeneity. If the subcutaneous placebo effect was underestimated, this would counter some of the bias due to violations in the transitivity assumption. Thus, the overall impact of the possible violation in the transitivity assumption, coupled with biases in the estimated placebo effect on the conclusions of the NMA, is uncertain, though it is notable that the 1 outcome that showed a significant positive effect for APO SL, change in UPDRS or MDS-UPDRS at 90 minutes, was the 1 comparison that relied solely on the APO SC study that estimated a larger subcutaneous placebo effect compared with the sublingual placebo effect in CTH-300.

Summary

The SLR conducted by the authors resulted in 8 studies being included in the ITC for APO SL (Kynmobi) and APO SC (Movapo). Two studies compared APO SL with placebo, 6 studies compared APO SC with placebo, and there were no studies that directly compared APO SL with APO SC. The implementation of the SLR was appropriately thorough and broad and provided an up-to-date body of evidence available for comparing APO SL with APO SC. However, with so few studies available for comparison, many of which had small sample sizes, the strength of the evidence for drawing firm conclusions regarding comparative effectiveness and safety is limited. This limitation is evident from the number of outcomes, most notably the safety outcomes, which could not be compared due to the sparsity of the network in addition to other limitations.

Among outcomes compared through the NMA, evidence was found that APO SL provides a less robust effect on hypomobility at 20 to 30 minutes after exposure compared with APO SC. No evidence was found for a difference in the effects of APO SL and APO SC on hypomobility at 60 minutes post exposure. At 90 minutes, evidence for a larger effect on hypomobility was found for APO SL compared with APO SC. The observed results were consistent with the pharmacokinetic profile of the 2 drugs, which has shown the concentration of APO to peak later for APO SL, around 40 minutes post exposure, and last longer. However, these results did not translate into a clear difference between the 2 drugs in the mean duration of ON per treated episode.

In addition to concerns about the sparse network used for the comparison, the comparison between APO SL and APO SC had many other limitations. The studies included in the comparison had numerous sources of heterogeneity across key variables, analytic shortcomings, differences in outcome measurement approaches, and differences in the comparator used to anchor the NMA. The majority of these limitations generally add uncertainty to the conclusions drawn from these comparisons e.g., network sparsity, unexplained study exclusions, study heterogeneity due to race and region, inadequate reporting on assessment of model convergence, and use of UPDRS motor scores versus MDS-UPDRS motor scores with sparse and differing time points. There were some limitations that likely biased specific analyses conservatively for APO SL, e.g., variation in study duration, studies recruiting patients with previous long-term exposure to apomorphine, studies titrating placebo patients on placebo, study differences in daily levodopa dose, and overestimation of the duration of ON for 1 APO SC study. However, there is also potential for anti-conservative bias for APO SL due to the differing administrative approaches used in the placebo arms, which could result in violations in the transitivity assumption for the NMA.

Other Relevant Evidence

This section includes the submitted long-term extension studies and additional relevant studies included in the sponsor's submission to CADTH that were considered to address important gaps in the evidence included in the systematic review.

Long-term Extension Studies

CTH-301 was a multi-centre, phase III, open-label, single-arm study evaluating the LTS and efficacy of APO SL in patients with PD who responded to levodopa therapy but still experienced OFF episodes.[51] Patients could be eligible for CTH-301 if they had completed CTH-201, CTH-203, CHT-300, CTH-301, or CTH-302 (rollover patients) and if, in the opinion of the investigator, they would benefit from continued treatment with APO SL, or they had not previously participated in a study with apomorphine (de novo patients) but met the selection criteria presented in Table 20.

CTH-301 is ongoing and is expected to be completed in July 2020. At the time of this review, all data available to CDR were collected by the data cut-off date (May 10, 2019).

Table 20: Key Selection Criteria of CTH-301

Inclusion criteria	Exclusion criteria
De novo patients	
• Patients ≥ 18 years of age • Clinical diagnosis of idiopathic PD • Stage 1 to 3 on the modified Hoehn & Yahr scale in the ON state • Clinically meaningful response to levodopa with well-defined early-morning OFF episodes (investigator-determined) • ≥ 1 OFF episode per day with a total daily OFF time duration of ≥ 2 hours during the waking day (patient-reported); MMSE score > 25 • Receiving stable doses of levodopa plus carbidopa (IR, CR, or ER) for ≥ 4 weeks before study screening, or MAO-B inhibitors for ≥ 8 weeks	• Atypical or secondary parkinsonism • Previous treatment with neurosurgical procedure for PD, continuous APO SC infusion, levodopa plus carbidopa, APO SC ≤ 7 days prior to the initial screening • Currently taking selective 5-HT_3 antagonists, dopamine antagonists (excluding quetiapine and clozapine) or dopamine-depleting drugs • Hypersensitivity to apomorphine hydrochloride • Clinically significant medical, surgical, or laboratory abnormality • Major psychiatric disorders • Current suicidal ideation ≤ 1 year prior to the second screening or attempted suicide < 5 years • Cankers or mouth sores ≤ 30 days prior to the initial screening or other clinically significant oral pathology
Rollover patients	
• Completion of any of the following studies: CTH-201, CTH-203, CTH-300, or CTH-302 and a finding that they would benefit from continued treatment with APO SL • No major increases in concomitant PD medications since completion of any of the aforementioned studies	• Major psychiatric disorders • Clinically significant medical, surgical, or laboratory abnormality that would make study participation unsafe or make treatment compliance difficult • Receipt of any investigational medication or participation in any clinical trial since completing a previous study using apomorphine • Development of cankers or mouth sores since completing a previous clinical study using APO SL • Current suicidal ideation
CTH-301 completer	
• Completion of CTH-301 and a finding that they would benefit from continued treatment with APO SL	• Major psychiatric disorder • Any clinically significant medical, surgical, or laboratory abnormality that would make study participation unsafe or make treatment compliance difficult • Receipt of any investigational (i.e., unapproved) medication or participation in any clinical trial since completing CTH-301 • Development of cankers or mouth sores since completing CTH-301 • Current suicidal ideation

5-HT3 = 5-hydroxytryptamine-3; APO = apomorphine hydrochloride; CR = controlled release; ER = extended release; IR = immediate release; MAO-B = monoamine oxidase type B; MMSE = Mini-Mental State Examination; PD = Parkinson disease; SC = subcutaneous; SL = sublingual.

Source: CTH-301 interim Clinical Study Report.[51]

Methods

After screening, eligible patients (de novo and rollover) enter the dose titration phase to determine an effective dose that could be administered in the LTS phase for treating OFF episodes. In the morning of the first day of titration, patients arrive at the clinic after their usual morning dose of PD medications but before taking their next dose of medication. Their normal morning dose of levodopa (without adjunctive PD medication) is then administered in the clinic approximately 2 hours after their normally scheduled second dose

of PD medication. Following confirmation by both the investigator and the patient that they are in the OFF state, patients can start with 10 mg of APO SL. The dose of APO SL can be adjusted in 5 mg increments within 3 days, depending on the patient's response. The maximum dose is 35 mg. During the course of treatment, if the patient achieves a full ON state at a specific dose level within 45 minutes of drug administration, the dose titration phase is considered completed, and the patient proceeds to the LTS phase at this dose. If the patient does not show improvement in OFF state at a particular dose, they are required to return to the clinic within the next 3 days to assess the next higher dose of APO SL. If the patient cannot tolerate the OFF state and does not respond efficaciously to the investigating dose of APO SL, they are terminated from the study. Any patients who reach 35 mg at the last titration visit (the sixth visit) and do not show a full ON response within 45 minutes are terminated from the study. The dose titration is required to be completed within 21 days. Efficacy assessment (with MDS-UPDRS Part III) is performed prior to dosing, and at 15, 30, and 60 minutes after dosing. A safety assessment is performed prior to dosing and immediately after the 60-minute efficacy assessment.

During the dose titration phase visits, patients are allowed to receive rescue levodopa (with or without other adjunctive PD medication) at a dosage considered appropriate by the investigator to achieve a full ON state if, in the opinion of the investigator, the patient can no longer tolerate the OFF state at any point during the visit. If this occurs, patients can return to the clinic on another day to resume the titration with the next highest dose. If a dose of APO SL cannot be found that provides a full ON response, the patient is terminated from the study. At all titration visits, at the discretion of the patient or investigator, there could be a situation where the next highest dose might be evaluated at a subsequent titration visit following a full ON response in order to assess the potential for the next highest dose in inducing an improved full ON response. If this dose produces an improved ON response relative to the lower dose without impacting patient safety and tolerability, the higher dose is used during the LTS phase of the study. If the ON response is the same or worse, or this higher dose is not well tolerated, the previous dose is used during the LTS phase.

Following completion of the titration phase, patients enter the LTS phase (up to 21 days after the final titration visit) and receive open-label APO SL treatment. The strength of the self-administered APO SL ranges from 10 mg to 35 mg per dose and up to 5 doses are allowed per day. Anytime during the LTS phase, all concomitant PD medications must remain stable. If it is determined that a dose adjustment is required for the purpose of the patient's safety or lack of efficacy, the patient returns to the clinic and the dose can be reduced to the next lower level or increased to the next higher level. If, in the opinion of the investigator, the reduced dose will not be tolerated by the patients, they are discontinued from the study. Rescue levodopa may be given to patients at any point during the LTS phase if they can no longer tolerate the OFF state. Patients receive training on handling the sublingual films using a placebo film at the first visit of the LTS phase.

CTH-301 completer patients resume treatment with APO SL at the dose they were administered prior to completing CTH-301. If this dose is no longer effective, the patients return to the clinic for dose adjustment visits until an effective dose is established.

In the current research protocol, patients are required to return to the clinic for a safety and efficacy assessment at week 4, week 12, week 24, week 36, and week 48 during the first year of the LTS phase. After week 48, patients return to the clinic approximately 4 months later. From year 2 to year 5 of the LTS phase, patients return to the clinic every 4 months for a safety assessment only. If a patient continues in the study beyond year 5 of the LTS

phase, the protocol will be amended to accommodate additional visits. Patients may continue to participate in the study until the sponsor terminates the study or until APO SL becomes commercially available in the patient's country.

The primary end point is safety and tolerability evaluation, such as orthostatic hypotension, oropharyngeal, and dopaminergic AEs. The AE analysis will focus on the dopaminergic and oral AEs. Efficacy end points include: the mean change from pre-dose in MDS-UPDRS Part III score at 15, 30, and 60 minutes post dose at week 24, week 36, and week 48 of the LTS phase; the percentage of patients with a patient-rated full ON response within 30 minutes at week 24, week 36, and week 48 of the LTS phase; the change in PGI-I score post dosing; and the change in PDQ-39 and EQ-5D scores.

The baseline characteristics for patients who entered the extension period are summarized in Table 21. In general, the baseline patient characteristics were comparable between the rollover patients and de novo patients. However, the rollover patients had a longer history of PD, a longer time since motor fluctuations, and took more levodopa compared with the de novo patients, while the de novo patients experienced a longer OFF period compared with rollover patients.

Table 21: Summary of Baseline Characteristics in Study CTH-301 (Safety Population)

Baseline characteristic	Rollover (N = 78)	De novo (N = 347)
Age (years), mean (SD)	63.4 (8.40)	64.5 (8.99)
Gender, n (%)		
Male	55 (70.5)	226 (65.1)
Female	23 (29.5)	121 (34.9)
Race, n (%)		
American Indian or Alaska Native	0	1 (0.3)
Asian	0	4 (1.2)
Black or African American	2 (2.6)	8 (2.3)
Native Hawaiian or other Pacific Islander	1 (1.3)	0
White	75 (96.2)	333 (96.0)
Other	0	1 (0.3)
BMI (kg/m^2), mean (SD)	[redacted]	[redacted]
Time since diagnosis of PD (years), mean (SD)	9.63 (4.31)	8.26 (4.44)
Time since motor fluctuations started (years), mean (SD)	5.19 (4.26)	4.34 (3.73)
Type of OFF episodes, n (%)		
Morning akinesia	[redacted]	[redacted]
Wearing OFF	[redacted]	[redacted]
Delayed ON	[redacted]	[redacted]
Dose failure	[redacted]	[redacted]
Sudden OFF	[redacted]	[redacted]
Number of OFF episodes per day, mean (SD)	4.1 (1.20)	3.9 (1.28)
Typical length of OFF episodes (minutes), mean (SD)	[redacted]	[redacted]
Total daily levodopa dose (mg), mean (SD)	1,478.14 (3,250.40)	1,119.93 (873.87)
Patients with ≥ 1 concomitant anti-PD medication, n (%)	[redacted]	[redacted]

Baseline characteristic	Rollover (N = 78)	De novo (N = 347)
Dopa and dopa derivatives	[redacted]	[redacted]
Dopamine agonists	[redacted]	[redacted]
MAO-B inhibitors	[redacted]	[redacted]
Amantadine derivatives	[redacted]	[redacted]
Pre-dose MDS-UPDRS Part III score at baseline, mean (SD)	[redacted]	[redacted]
MDS-UPDRS Part III score at baseline 30 minutes post dose, mean (SD)	[redacted]	[redacted]

BMI = body mass index; MAO-B = monoamine oxidase type B; MDS-UPDRS = Movement Disorders Society Unified Parkinson's Disease Rating Scale; NA = not applicable; PD = Parkinson disease; SD = standard deviation.

Source: CTH-301 interim Clinical Study Report.[51]

Statistical Analysis

The sample size of this study was not based on any power calculations. All data were summarized descriptively. No statistical testing was performed for this study, given its design and ongoing status. Change from baseline in the continuous efficacy end points will be estimated using the number of observations, mean SD, median, minimum, and maximum. Descriptive statistics for categorical data include frequency counts and percentages.

The safety population includes all patients who are enrolled in CTH-301 and receive 1 dose of the study drug. All patients who are enrolled and receive at least 1 dose of the study drug during the dose titration phase are included in the titration full analysis set. All patients who are enrolled and receive at least 1 dose of the study drug during the LTS phase are included in the LTS full analysis set. An efficacy analysis is conducted using the titration full analysis set and the LTS full analysis set.

Patient Disposition

As of the data cut-off date (May 10, 2019), 427 patients have been enrolled (78 rollover and 349 de novo). A total of 425 patients have received at least 1 dose of APO SL (78 rollover and 347 de novo) in the titration phase. A total of 345 patients received at least 1 dose of study drug during the LTS phase (70 rollover and 275 de novo) and have been included in the LTS phase safety population.

Among these patients, 6 rollover patients (7.7%) and 54 de novo patients (15.5%) discontinued the treatment in dose titration phase. During the LTS phase, 23 rollover patients (32.9%) and 149 de novo patients (54.2%) discontinued the treatment. The main reasons for discontinuation were AEs and consent withdrawal in both phases. De novo patients were more likely to withdraw treatment compared with the rollover patients. Details of patient disposition are provided in Table 22.

Table 22: Patient Disposition in CTH-301 (All Available Population)

Patient disposition	CTH-301	
	Rollover	De novo
Screened, N	499	
Dose titration phase		
Enrolled into the study, n (%)	78 (90.7)	349 (84.5)
Enrolled in dose titration phase and received ≥ 1 dose of APO SL, n (%)	78 (100)	347 (99.4)
Discontinued during dose titration, n (%)	6 (7.7)	54 (15.5)
Adverse events	3 (3.8)	23 (6.6)
Lack of efficacy	2 (2.6)	10 (2.9)
Protocol violation	0	4 (1.1)
Patient withdrew consent	1 (1.3)	15 (4.3)
Lost to follow-up	0	0
Death	0	0
Other	0	2 (0.6)
LTS phase		
Patients who received ≥ 1 dose of APO SL, n (%)	70 (89.7)	275 (78.8)
Discontinued during LTS phase, n (%)	23 (32.9)	149 (54.2)
Adverse events	16 (22.9)	90 (32.7)
Lack of efficacy	0	11 (4.0)
Protocol violation	0	2 (0.7)
Patient withdrew consent	6 (8.6)	37 (13.5)
Lost to follow-up	1 (1.4)	3 (1.1)
Death	0	1 (0.4)
Other	0	5 (1.8)

APO = apomorphine hydrochloride; LTS = long-term safety; SL = sublingual.

Source: CTH-301 interim Clinical Study Report.[51]

Exposure to Study Treatments

Rollover patients had longer duration of exposure to the study medication but used similar number of doses per day compared with de novo patients. Details of extent of exposure are provided in Table 23. In addition, during the dose titration phase and LTS phase, there were more rollover patients ([redacted]) reduced their doses due to AEs compared with de novo patients ([redacted]).

Table 23: Extent of Exposure

Exposure	Rollover	De novo
Duration of exposure, days, mean (SD) (LTS full analysis set)	N = 70	N = 275
	195.5 (172.40)	155.9 (146.34)
Average number of daily doses, n, mean (SD)[a] (LTS full analysis set)	[redacted]	[redacted]
	[redacted]	[redacted]
AEs leading to dose reduction, n (%) (safety population)	[redacted]	[redacted]
	[redacted]	[redacted]

AE = adverse event; LTS = long-term safety; SD = standard deviation.

[a] Average number of daily doses is calculated as the average number of daily doses per patient during the days in which dosing information was recorded.

Source: CTH-301 interim Clinical Study Report.[51]

Results

Safety

Adverse Events

In the dose titration phase plus LTS phase, AEs were reported in 359 patients (84.5%) in overall population: 66 rollover patients (84.6%) and 293 de novo patients (84.4%). The majority of the AEs were considered mild to moderate in severity. Overall, in the safety population, 4.5% of TEAEs were severe; 12 (15.4%) rollover patients experienced 24 (6.9%) severe TEAEs, and 37 (10.7%) de novo patients experienced 62 (4.0%) severe TEAEs. The most common AEs reported by the study participants were gastrointestinal disorders (51.5%), followed by nervous system disorders (43.5%); respiratory, thoracic, and mediastinal disorders (20.9%); general disorders and administration-site conditions ([redacted]); infection and infestations ([redacted]); injury, poisoning, and procedural complications (14.4%); vascular disorders ([redacted]); musculoskeletal and connective tissue disorders ([redacted]); and psychiatric disorders ([redacted]).

Serious Adverse Events

Overall, 35 (8.2%) patients experienced SAEs, including 8 (10.3%) rollover patients and 27 (7.8%) de novo patients. The most commonly reported SAEs were cardiac system disorders (7 patients, 1.6%), nervous system disorders (7 patients, 1.6%), and injury, poisoning, and procedural complications (6 patients, 1.4%).

Withdrawal Due to Adverse Event

The incidence of AEs leading to drug withdrawal was lower in rollover patients (19 patients, 24.4%) versus de novo patients (111 patients, 2.0%).

Mortality

Four deaths occurred during the study, 1 in the dose titration phase and 3 in the LTS phase. Three de novo patients died: 1 due to cardiac arrest, 1 due to drowning, and 1 due to sepsis. One rollover patient died of cardio-respiratory arrest and pneumonia. No deaths were considered be treatment related, except for the patient who died of sepsis. For this patient, the relationship of the death to the study treatment was considered “unlikely.”

Notable Harms

In CTH-301, the reported AEs of special interest included stomatitis, oral ulcers, oral irritation, or allergic or sensitivity response to the formulation ([redacted]), falls and injuries ([redacted]), hypotension ([redacted]), daytime sudden onset of sleep (14.4%), dyskinesias (6.6%), and syncope (3.1%). The risks of falls and injuries, hypotension, and syncope were higher in the rollover patients compared with the de novo patients. Occurrence of impulsive behaviour was not reported by the data cut-off.

Details of the AEs in Study CTH-301 are presented in Table 24.

Table 24: Harm Outcomes Occurring During the Dose Titration Phase Plus LTS Phase (Safety Population)

Harms	Rollover (N = 78)	De novo (N = 347)	Overall (N = 425)
Any TEAEs, n (%)	**66 (84.6)**	**293 (84.4)**	**359 (84.5)**
Gastrointestinal disorders	43 (55.1)	176 (50.7)	219 (51.5)
Nervous system disorders	31 (39.7)	154 (44.4)	185 (43.5)
Infections and infestations	[redacted]	60 (17.3)	76 (17.9)
General disorders and administration-site conditions	[redacted]	71 (20.5)	85 (20.0)
Respiratory, thoracic, and mediastinal disorders	[redacted]	72 (20.7)	89 (20.9)
Injury, poisoning, and procedural complications	[redacted]	45 (13.0)	61 (14.4)
Musculoskeletal and connective tissue disorders	[redacted]	39 (11.2)	47 (11.1)
Psychiatric disorders	[redacted]	37 (10.7)	47 (11.1)
Investigations	[redacted]	34 (9.8)	39 (9.2)
Vascular disorders	[redacted]	47 (13.5)	57 (13.4)
SAEs, n (%)	**8 (10.3%)**	**27 (7.8%)**	**35 (8.2)**
WDAEs, n (%)	**19 (24.4)**	**111 (32.0)**	**130 (30.6)**
Death, n (%)	**1 (1.3)**	**3 (0.9)**	**4 (0.9)**
	• Cardio-respiratory arrest or pneumonia: 1	• Cardiac arrest: 1 • Drowning: 1 • Sepsis: 1	
AEs of special interest, n (%)	[redacted]	[redacted]	[redacted]
Stomatitis, oral ulcers, oral irritation, or allergic or sensitivity response to the formulation	[redacted]	[redacted]	[redacted]
Falls and injuries	[redacted]	[redacted]	[redacted]
Hypotension, orthostatic hypotension	[redacted]	[redacted]	[redacted]
Daytime sudden onset of sleep	[redacted]	[redacted]	[redacted]
Dyskinesias	[redacted]	[redacted]	[redacted]
Syncope	[redacted]	[redacted]	[redacted]

AE = adverse event; LTS = long-term safety; SAE = serious adverse event; TEAE = treatment-emergent adverse event; WDAE = withdrawal due to adverse event.

Source: CTH-301 interim Clinical Study Report.[51]

Efficacy

Change in MDS-UPDRS Part III Score at Week 24

In Study CTH-301, the change in MDS-UPDRS Part III score from pre-dose to 30 minutes post dose was a secondary end point. During the LTS phase, the mean decrease in MDS-UPDRS Part III score from pre-dose to 30 minutes post dose overall was [redacted] points on day 1, [redacted] points at month 3, and [redacted] points at month 6 (Table 25).

Table 25: Change in MDS-UPDRS Part III Score From Pre-Dose to 30 Minutes Post Dose in LTS Phase (LTS Full Analysis Set)

Visit	Overall population (N = 345)
LTS day 1, mean (SD)	[redacted]
LTS month 3, mean (SD)	[redacted]
LTS month 6, mean (SD)	[redacted]

LTS = long-term safety; MDS-UPDRS = Movement Disorders Society Unified Parkinson's Disease Rating Scale; SD = standard deviation.

Source: CTH-301 interim Clinical Study Report.[51]

Percentage of Patients Achieving a Full ON Response 30 Minutes Post Dose

During the LTS phase of the study, most patients had an observed ON response within 30 minutes post dose at every LTS visit (Table 26).

Table 26: Patients Achieving a Patient-Rated Full ON Response 30 Minutes Post Dose in LTS Phase (LTS Full Analysis Set)

Visit	Observed ON response < 30 minutes	Kynmobi (n = 345)
LTS day 1, mean (SD)	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
LTS month 3, mean (SD)	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
LTS month 6, mean (SD)	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]

LTS = long-term safety; SD = standard deviation.

Source: CTH-301 interim Clinical Study Report.[51]

Results of other efficacy outcomes (e.g., assessment of PGI-I) or patient-reported outcomes (e.g., PDQ-39 and EQ-5D) were not available at the time of this review.

Critical Appraisal

The main limitation for Study CTH-301 is there is no control group. The study is still ongoing. Patients may continue to participate in the study until the sponsor terminates it or until APO SL is commercial availability in the patient's country. Therefore, study duration is unknown. Even though CTH-301 was designed as a long-term study, the available efficacy

and safety data were collected by the data cut-off on May 10, 2019. Results on week 24 are not considered sufficient, given that PD is a chronic, progressive condition and the treatment effect of the study drug on the patient's physical and mental well-being needs to be explored over the long run. In addition, results of a number of efficacy outcomes were not available at this time point. By data cut-off, there were patients who had received APO SL for more than 24 weeks. Based on the interim report for CTH-301, 64 patients have received APO SL for longer than 12 months, and 32 patients had results from week 48.

Discussion

Summary of Available Evidence

One phase III, multi-centre, double-blind, placebo-controlled superiority RCT, CTH-300 (N = 109), met the inclusion criteria for this systematic review. The primary objective of CTH-300 was to evaluate the efficacy and safety of APO SL versus placebo in patients with PD over a 12-week period. The trial included adult patients with idiopathic PD, with a clinically meaningful response to levodopa therapy and with at least 1 OFF episode per day. It contained 2 phases. In the open-label dose titration phase, patient's response to single, escalating doses of APO SL (started at 10 mg and increased in 5 mg increments to a maximum dose of 35 mg) was evaluated in an outpatient setting to determine the dose that would be used in the next phase, a double-blind maintenance treatment phase. Any patients who reached 35 mg at the last titration visit (the sixth visit) and did not exhibit a full ON response within 45 minutes were terminated from the study. Patients who completed the dose titration phase entered the maintenance treatment phase and were randomly assigned to 12-week treatment with APO SL or placebo. Although an appropriate method of blinding has been used for treatment concealment, it may have been difficult to maintain blinding of treatments due to the obvious change in PD symptoms and potential AEs from treatment, particularly for patients who had received previous apomorphine therapy (2.1% of the safety population received prior apomorphine therapy). Reporting of patient-rated outcomes, such as HRQoL, symptom reductions, and some of the harm outcomes may have been biased. Among the 141 patients who entered the dose titration phase, 109 completed this phase and were randomized to the study drugs. In general, the 2 treatment groups were similar in patients' baseline characteristics, except there were more male patients in the APO SL group and those in the APO SL group had shorter disease duration (0.6 years difference) compared with placebo. During the maintenance phase, 37% of the APO SL–treated patients and 16% of the placebo-treated patients discontinued the treatment. The main reason for withdrawal was AEs, 28% in the APO SL group and 9% in the placebo group. The average number of daily doses was 2.2 in the APO SL group and 2.5 in the placebo group. The primary efficacy end point was change in hypomobility, measured with the mean change from pre-dose MDS-UPDRS Part III score at 30 minutes post dose at week 12 visit. Other efficacy outcomes in CTH-300 included frequency of patient-rated post-dose ON response, change in PD symptoms (e.g., sleepiness disorder) and HRQoL. The safety profile of APO SL was examined, as well.

A hierarchical testing approach was used for the analyses of the primary and secondary efficacy end points to control the familywise type I error rate to ≤ 5%. Ten efficacy end points, including the primary and key secondary end points, were included in this procedure (see Statistical Analysis section for a full list of efficacy end points included in the hierarchy). Statistical significance was not achieved for the efficacy end points ranked third in the hierarchical testing; therefore, statistical significance cannot be formally claimed for any of the end points ranked after this end point. Such end points included:

- percentage of patients at week 12 with a patient-rated full ON response within 30 minutes post dose that had a duration of at least 30 minutes
- PGI-I assessment
- mean change from screening to week 12 in MDR-UPDRS Part II score

- percentage of instances where a full ON response was achieved at 30 minutes post dose, based on the home dosing diary entries during the 2 days prior to week 12 visit
- mean change from screening to week 12 in PDQ-39 summary index score
- time to when study drug was starting to have an effect at week 12.

One of the major limitations of CTH-300 was the substantial missing data in the trial, in particular, in the APO SL arm. Findings of the study could be biased and it makes results uncertain. Sensitivity analyses were conducted to evaluate the impact of missing data on study findings. Results of the sensitivity analyses for missing data handling supported the findings from the primary analysis.

Interpretation of Results

Efficacy

The primary end point was mean change from pre-dose to 30 minutes post dose MDS-UPDRS Part III score at week 12 in the mITT population. The results showed the LS mean change from pre-dose to 30 minutes post dose MDS-UPDRS Part III score for the APO SL group was significantly lower compared with placebo, and the LS mean treatment difference (APO SL minus placebo) was −7.6 points (95% CI, −11.5 to −3.7; P = 0.0002). This was considered a clinically significant change according to both the clinical expert and the MCID for MDS-UPDRS Part III. The results of the sensitivity analyses for missing data handling supported the findings from the primary analysis. The results of the pre-specified subgroup analyses of the primary end point, based on age, race, baseline pre-dose MDS-UPDRS Part III score (greater than median versus less than median), or dose assigned, were generally consistent with those from the primary analyses, but these results were limited by small sample sizes. Note that there was no adjustment for multiplicity in the subgroup analyses.

Additional outcomes were measured as secondary end points, such as percentage of patients with a full ON response within 30 minutes at week 12, PGI-I, mean change from baseline to week 12 in PDQ-39, and time to effect. The “percentage of patients with a patient-rated full ON response within 30 minutes post dose at week 12” was the key secondary end point in CTH-300 and ranked second in the hierarchy. A statistically significant difference was observed in favour of APO SL versus placebo in the percentage of patients achieving a full ON response within 30 minutes post drug administration at week 12 (the predicted response rate was 35% for APO SL versus 16% for placebo; adjusted odds ratio: 2.81; 95% CI, 1.04 to 7.64; P = 0.0426). The percentage of patients with a full ON response post dose with a duration of at least 30 minutes at week 12 was 31% in the APO SL group and 14% in the placebo group; however, no statistically significant difference was detected for this outcome (adjusted odds ratio, 2.80; 95% CI, 1.00 to 7.84; P = 0.0501). The between-group difference in change from baseline in the PDQ-39 summary index score at week 12 was not statistically significant: 0.31 for APO SL versus −1.67 for placebo (mean difference, 1.98; 95% CI, −2.16 to 6.12; P = 0.3447). Patients treated with APO SL (37%) were more likely to report “improved” than those treated with placebo (20%) at week 12. The median time to when study medication started to have an effect at week 12 was 21 minutes for APO SL, while it was not estimable in the placebo group.

Change in sleepiness disorders measured with ESS was numerically similar between APO SL and placebo. The change in the ESS summary score at week 12 was 0.5 and −0.6 for APO SL and placebo, respectively. The change in EQ-5D-5L health index score was −0.03

and 0 for APO SL and placebo, respectively. Note that change in ESS and EQ-5D-5L were not adjusted for multiplicity.

Results of the efficacy analyses suggest a statistically and clinically significant improvement in motor fluctuations measured with MDS-UPDRS Part III score. This is a commonly used, validated tool to assess the treatment effect in patients with PD. In addition, significantly more patients treated with APO SL achieved a full ON response 30 minutes after dosing compared with placebo. Patients in the APO SL group were more likely to indicate improvement in the disease after treatment compared with the placebo group. However, such benefits did not translate into a gain in HRQoL in the study population at week 12. Short study duration may partially explain this discrepancy.

An ongoing, open-label, uncontrolled, LTS study (Study CTH-301) explored the long-term safety and clinical effectiveness of APO SL up to 48 weeks of treatment in PD patients with or without previous APO SL therapy. The study findings suggested that as of data cut-off (May 10, 2019), the improvements in motor function (measured with MDS-UPDRS Part III score) that were observed 24 weeks after study commencement were maintained. Due to the nature of the single-arm study, the findings should be interpreted with caution.

In the absence of head-to-head trial data comparing APO SL with other active treatments for OFF episode management, the sponsor conducted an indirect analysis based on a systematic review of RCTs and compared the efficacy and safety of APO SL with APO SC (Movapo). The evidence supported APO SL having a less robust effect on hypomobility between 20 and 30 minutes after drug administration, with a potentially superior effect after 90 minutes compared with APO SC. Key limitations of the ITC included a sparse network and study differences in design and patient characteristics. Therefore, results of the comparative effectiveness between APO SL and APO SC should be interpreted with caution.

Harms

In CTH-300, the frequency of TEAEs during the dose titration phase was 58.2%. During the double-blind maintenance treatment phase, the frequency of TEAEs was higher (88.9%) in the APO SL group compared with the placebo group (45.5%). The majority of AEs were considered mild to moderate. The most common AEs reported with APO SL were gastrointestinal disorders ([redacted] during the dose titration phase; APO SL [redacted] versus placebo [redacted] during the maintenance treatment phase), followed by nervous system disorders ([redacted] during the dose titration phase; APO SL [redacted] versus placebo [redacted] during the maintenance treatment phase), respiratory, thoracic, and mediastinal disorders (APO [redacted] versus placebo [redacted] during the maintenance phase), general disorders and administration-site conditions (APO SL [redacted] versus placebo [redacted] during the maintenance treatment phase), and psychiatric disorders (APO SL [redacted] versus placebo [redacted] during the maintenance treatment phase). Isolated cases of SAEs were reported: 1 in the titration phase and 3 in the maintenance treatment phase (2 [3.7%] with APO SL and 1 [1.8%] with placebo). Patients treated with APO SL were more likely to withdraw from treatment because of AEs (27.8% for APO SL versus 7.3% for placebo) during the maintenance treatment phase. One patient treated with APO SL 15 mg died during the maintenance treatment phase, and the death was considered possibly related to treatment.

In terms of harms of particular interest, the occurrence of gastrointestinal disorders, application-site reactions (such as stomatitis, oral ulcers, and oral irritation), allergic or

sensitivity response to the formulation, daytime sudden onset of sleep, falls and injuries, and hypotension were higher in APO SL–treated patients compared with placebo.

An ongoing, uncontrolled, single-arm, LTS study (Study CTH-301) provided safety data up to week 48. The results suggested that for PD patients with or without previous APO SL therapy, the safety profile of APO SL at data cut-off (May 10, 2019) was generally consistent with that observed in Study CTH-300 (pivotal study of this review, providing safety data up to week 12), with no unexpected safety signals. Due to the nature of the single-arm study, the LTS findings should be interpreted with caution.

In the sponsor-submitted NMA, the authors indicated that safety results could not be formally compared between APO SL and APO SC, primarily due to study heterogeneity. Conclusions regarding the safety of Kynmobi versus Movapo cannot be drawn from this NMA.

Conclusions

One randomized, double-blind, placebo-controlled trial provides evidence on the efficacy and safety of APO SL as an acute, intermittent treatment for OFF episodes in patients with PD. Overall, after 12 weeks of treatment with APO SL, a statistically significant and clinically meaningful improvement in motor function was observed compared with placebo. Improvement in motor function was measured with change in MDS-UPDRS Part III score from pre-dose to 30 minutes post dose. In addition, treatment with APO SL was associated with more frequent patient-rated full ON response, more patient-indicated improvement in disease, and shorter time to effect compared with placebo. However, the differences between APO SL and placebo in change in HRQoL or symptom relief were not significant in the study population. Results of an ITC analysis comparing APO SL with APO SC suggest the former was associated with a smaller improvement on hypomobility between 20 and 30 minutes after drug administration but had a potentially superior effect after 90 minutes, compared with the latter. However, results of the comparative effectiveness between sublingual and subcutaneous apomorphine in this analysis should be interpreted with caution due to the major limitations of those results.

The incidence of AEs was higher in patients treated with APO SL compared with placebo after 12 weeks of treatment. The common AEs include gastrointestinal disorders; nervous system disorders; respiratory, thoracic, and mediastinal disorders; psychiatric disorders; and infections. The AEs were mostly mild to moderate in severity. SAEs were not frequently reported in CTH-300. Patients treated with APO SL were more likely to withdraw from treatment due to AEs compared with placebo. An ongoing single-arm LTS study confirms the safety profile of APO SL up to week 48.

Appendix 1: Literature Search Strategy

Clinical Literature Search

OVERVIEW	
Interface:	Ovid
Databases:	MEDLINE All (1946-present) Embase (1974-present) **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	July 9, 2020
Alerts:	Bi-weekly updates until project completion
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
.fs	Floating subheading
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 character
?	Truncation symbol for one or no characters only
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.mp	Mapped term
.rn	Registry number
.yr	Publication year
.jw	Journal word title
freq=#	Requires terms to occur # number of times in the specified fields
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily
cctr	Ovid database code; Cochrane Central Register of Controlled Trials

MULTI-DATABASE SEARCH STRATEGY	
Line #	**Searches Strategy**
1	(Kynmobi* or APL-130277 or APL130277).ti,ab,kf,ot,hw,nm,rn.
2	apomorphine/
3	(9K13MD7A0D or N21FAR7B4S or F39049Y068).rn,nm.
4	(Apokyn* or Apomorphin* or apomorfin* or Apowok* or Spontane or ApoGo or Apo Go or Uprima* or Ixense* or Britaject* or Apokinon* or apofin* or Apomine* or Apskyn* or Dacepton* or Datsepton* or dopaceptin* or Taluvian* or Movapo* or Zyprima* or pomorphini hydrochloridium* or "vr 004" or vr004 or vr040 or "vr 040" or vr 400).ti,ab,kf,ot,hw,nm,rn.
5	("EINECS 206 243 0" or EINECS 2062430 or EINECS2062430 or EINECS 200-360-0 or EINECS 2003600 or NSC 11442 or NSC11442 or HSDB 3289 or HSDB3289).ti,ab,kf,ot,hw,nm,rn.
6	2 or 3 or 4 or 5
7	Administration, Sublingual/ or exp Tongue/ or Mouth Mucosa/ or Administration, Buccal/
8	(subling* or sub-ling* or supraling* or supra-ling* or tongue* or buccal* or transbuccal* or trans-buccal* or transmucosa* or trans-mucosa* or mucosa* or intrabuccal*).ti,ab,kf.
9	7 or 8
10	6 and 9
11	1 or 10
12	11 use medall
13	(Kynmobi* or APL-130277 or APL130277).ti,ab,kw,dq.
14	*apomorphine/
15	(Apokyn* or Apomorphin* or apomorfin* or Apowok* or Spontane or ApoGo or Apo Go or Uprima* or Ixense* or Britaject* or Apokinon* or apofin* or Apomine* or Apskyn* or Dacepton* or Datsepton* or dopaceptin* or Taluvian* or Movapo* or Zyprima* or pomorphini hydrochloridium* or "vr 004" or vr004 or vr040 or "vr 040" or vr 400).ti,ab,kw,dq.
16	("EINECS 206 243 0" or EINECS 2062430 or EINECS2062430 or EINECS 200-360-0 or EINECS 2003600 or NSC 11442 or NSC11442 or HSDB 3289 or HSDB3289).ti,ab,kw,dq.
17	14 or 15 or 16
18	exp Buccal Drug Administration/ or exp Tongue/ or exp Mouth Mucosa/ or Buccal Mucosa/
19	(subling* or sub-ling* or supraling* or supra-ling* or tongue* or buccal* or transbuccal* or trans-buccal* or transmucosa* or trans-mucosa* or mucosa* or intrabuccal*).ti,ab,kw.
20	18 or 19
21	17 and 20
22	13 or 21
23	22 use oemezd
24	(conference abstract or conference review).pt.
25	23 not 24
26	12 or 25
27	remove duplicates from 26

CLINICAL TRIAL REGISTRIES	
ClinicalTrials.gov	Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials. Search updated prior to the completion of stakeholder feedback period Search terms: kynmobi or apomorphine hydrochloride and Parkinson's disease
WHO ICTRP	International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials. Search updated prior to the completion of stakeholder feedback period. Search terms: kynmobi or apomorphine hydrochloride and Parkinson's disease]

OTHER DATABASES	
PubMed	Searched to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.

Grey Literature

Search dates:	July 6 – July 8, 2020
Keywords:	kynmobi or apomorphine hydrochloride and Parkinson's disease
Limits:	None

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
- Clinical Trial Registries
- Databases (free)
- Health Statistics
- Internet Search
- Open Access Journals.

Appendix 2: Detailed Outcome Data

Sensitivity analyses of the primary efficacy end point were conducted to verify the robustness of the primary analysis and to examine the missing data assumptions of the primary analysis. The results of the pre-specified sensitivity analyses were consistent with those observed in the mITT population. Details of the sensitivity analyses are provided in Table 27.

Table 27: Change in MDS-UPDRS Part III Score From Pre-Dose to 30 Minutes Post Dose at Week 12 (Sensitivity Analyses)

Assumptions	APO SL Mean (SE)	Placebo Mean (SE)	LS mean difference (APO SL minus placebo), estimate (95% CI)	P value
Completer population	[redacted]	[redacted]	[redacted]	[redacted]
Per-protocol population	[redacted]	[redacted]	[redacted]	[redacted]
MIA with missing-at-random assumption (mITT population)[a]	[redacted]	[redacted]	[redacted]	[redacted]
MIA with missing-not-at-random assumption (placebo group–based imputation) (mITT population)[b]	[redacted]	[redacted]	[redacted]	[redacted]
MIA with missing-not-at-random assumption (tipping point approach) (mITT population)[c] Value of delta: 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5 8.0 8.5	[redacted]	[redacted]	[redacted]	[redacted]
Comparability of pre-dose values (mITT population)[d]	[redacted]	[redacted]	[redacted]	[redacted]
LOCF (mITT population)[e]	[redacted]	[redacted]	[redacted]	[redacted]
Responder analysis (mITT population)[f]	[redacted]	[redacted]	[redacted]	[redacted]

APO = apomorphine hydrochloride; CI = confidence interval; LOCF = last observation carried forward; LS = least squares; MDS-UPDRS = Movement Disorders Society Unified Parkinson's Disease Rating Scale; MIA = multiple imputation analysis; mITT = modified intention to treat; SE = standard error; SL = sublingual.

[redacted]

Source: CTH-300 Clinical Study Report.[15]

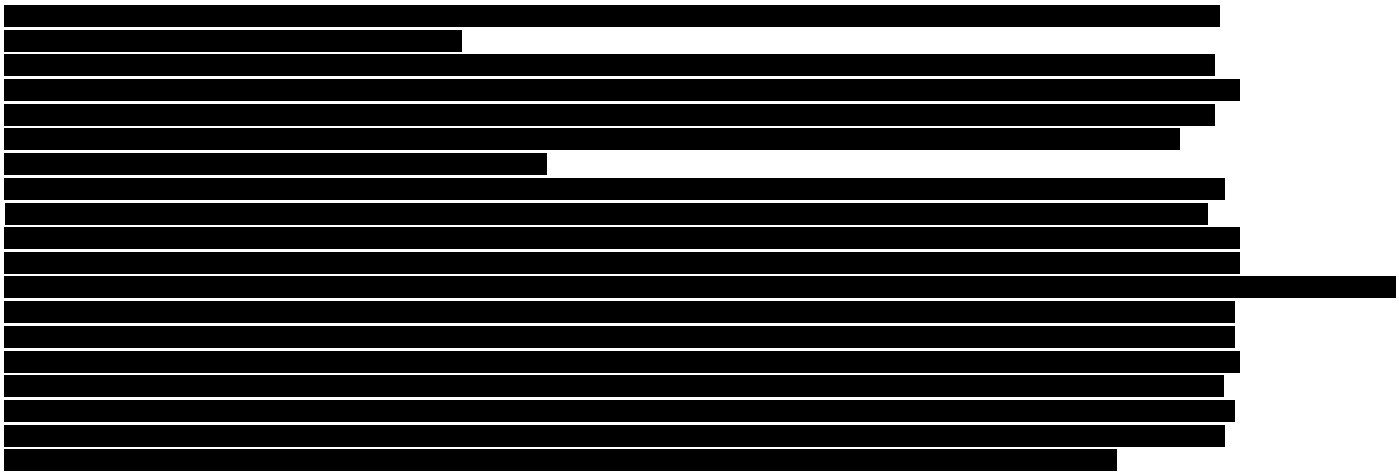
Pre-specified subgroup analyses were conducted on the primary end point (change in MDS-UPDRS Part III score from pre-dose to 30 minutes post dose at week 12) based on age, race, gender, dose assigned, and baseline pre-dose MDS-UPDRS Part III score. None of these variables were stratified in randomization. The comparability of patient characteristics within the subgroups at baseline was not reported. The results of the subgroup analyses were consistent with the primary analyses. There was no adjustment for multiplicity in the subgroup analyses. Details of the subgroup analyses are presented in Table 28.

Table 28: Change in MDS-UPDRS Part III Score (Mean, SE) From Pre-Dose to 30 Minutes Post Dose at Week 12 (Subgroup Analyses)

Subgroups		APO SL	Placebo	LS mean difference (APO SL minus placebo), estimate (95% CI)	P value
Dose assigned[a]					
Baseline pre-dose MDS-UPDRS Part III score[b]					

Subgroups		APO SL	Placebo	LS mean difference (APO SL minus placebo), estimate (95% CI)	P value

APO =apomorphine hydrochloride; CI = confidence interval; MDS-UPDRS = Movement Disorders Society Unified Parkinson's Disease Rating Scale; SE = standard error; SL = sublingual.



Source: CTH-300 Clinical Study Report.[15]

Appendix 3: Description and Appraisal of Outcome Measures

Aim

To summarize the validity of the following outcome measures:

- MDS-UPDRS
- PDQ-39
- ESS
- EQ-5D-5L

Findings

Table 29: Validity and Minimal Important Differences of Outcome Measures

Instrument	Type	Evidence of validity?	MCID	References
Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS)	A measure of disability and impairment in PD that was updated from the original UPDRS. It consists of 4 parts with each individual item scored between 0 (normal) and 4 (severe): • Part I (non-motor experiences of daily living: 13 items [6 rater-based and 7 patient self-assessments]) • Part II (motor experiences of daily living; 13 patient-based items) • Part III (motor examination; 18 items with 33 scores due to body distribution scores [right, left, or other]) • Part IV (motor complications; 6 items relating to dyskinesia and fluctuations)	Yes	Part III: • 3.25 points for improvement • 4.63 points for worsening	Goetz et al. (2008)[52] Martinez-Martin et al. (2013)[53] Horvath et al. (2015)[26] Horvath et al. (2017)[54] Makkos et al. (2018)[55]
Parkinson's Disease Questionnaire 39 (PDQ-39)	The PDQ-39 is a disease-specific HRQoL measure consisting of 8 domains (mobility, ADL, emotional well-being, stigma, social support, cognition, communication, and bodily discomfort) graded on a 5-point scale (0 = never, 4 = always)	Yes	Total score: −1.6 Subscores:	Peto et al. (2001)[35] Peto et al. (1995)[30] Peto et al. (1998)[56] Jenkinson et al. (1997)[31] Jenkinson et al. (2003)[57] Harrison et al. (2000)[58]

Instrument	Type	Evidence of validity?	MCID	References
			• mobility: −3.2 • ADL: −4.4 • emotional well-being: −4.2 • stigma: −5.6 • social support: −11.4 • cognition: −1.8 communications: −4.2 • pain: −2.1	
Epworth Sleepiness Scale (ESS)	The ESS assesses a patient's sleepiness during the day during different daily activities. The total score ranges from 0 to 24, with higher scores indicating greater sleep propensity	Yes	Not identified	Hagell and Broman (2007)[28]
EuroQol 5-Dimensions 5-Levels questionnaire (EQ-5D-5L)	EQ-5D-5L is a general, non–disease-specific HRQoL questionnaire	Some	• Summarized mean index score of 0.056 (SD, 0.011) and summarized median index score of 0.056 (IQR, 0.049 to 0.063) for general use • No PD-specific MCID identified	McClure et al. (2017)[59] Alvarado-Balanos et al. (2015)[38]

ADL = activities of daily living; EQ-5D-5L = EuroQol 5-Dimensions 5-Level questionnaire; ESS = Epworth Sleepiness Scale; HRQoL = health-related quality of life; IQR = interquartile range; MDS-UPDRS = Movement Disorder Society Unified Parkinson's Disease Rating Scale; MCID = minimal clinically important difference; PD = Parkinson disease; PDQ-39 = Parkinson's Disease Questionnaire 39; SD = standard deviation.

Movement Disorder Society Unified Parkinson's Disease Rating Scale

The MDS-UPDRS is the updated version of the original UPDRS and is the standard instrument for measuring parkinsonian signs and symptoms. Despite the comprehensive coverage of motor symptoms and wide utilization of the UPDRS, there were a few notable weaknesses noted by the Movement Disorders Society, including limited non-motor screening items, "flaws and ambiguities" for some items, and inadequate instructions for raters.[60] The Society commissioned a revision of the original scale in 2007. The UPDRS revision sponsored by the Movement Disorders Society demonstrated improved psychometric properties in different settings, in addition to providing a large-scale comparison with the original version.[52]

The MDS-UPRDS scale comprises 4 parts: Part I (non-motor experiences of daily living; 13 items [6 rater-based and 7 patient self-assessments]), Part II (motor experiences of daily living; 13 patient-based items), Part III (motor examination; 18 items with 33 scores associated with body distribution scores [right, left, or other]), and Part IV (motor complications; 6 items relating to dyskinesia and fluctuations).[52] A total of 65 items are rated and are written at a seventh-grade level for ease of comprehension. There were 9

new items added to the updated MDS-UPDRS: anxious mood, dopamine dysregulation syndrome, urinary problems, constipation, fatigue, doing hobbies, getting in and out of bed, toe tapping, and freezing.[52] Rater-based assessments are performed via interview and, in total, take no more than 30 minutes to complete. The other patient-based sections can be answered solely by the patient or caregiver; however, the physician should be available for consultation in the event something is not clear. All questions are now scored on a 5-point scale, with 0 = normal, 1 = slight (low frequency or intensity and no impact on function), 2 = mild (symptoms or signs of frequency and intensity with a modest functional impact), 3 = moderate (symptoms or signs of sufficient frequency and intensity to impact but not prevent function), and 4 = severe (symptoms or signs that prevent function).[52] There were 2 main reasons for the shift from the original scale construct, from mild, moderate, severe, or marked to slight, mild, moderate, or severe. The first was that clinical trials generally assess patients early in their disease; therefore, there was a need to distinguish more between normal, slight, and mild problems. The second reason was because the functional differences between severe and marked (in the old UPDRS) may not be as clinically relevant, since both of these scores indicate high functional impairment. Detailed instructions are also now included with the MDS-UPDRS, with the hope that this will limit variability in what is being examined and standardize the process.[52]

Goetz et al.[52] assessed the MDS-UPDRS in relation to the former UPDRS in 877 English-speaking patients (from the UK, Canada, and the US) with confirmed PD (all Hoehn & Yahr stages were represented; the majority of patients were classified as stage 2 or 3). Strong concurrent validity between the 2 total scores was evident (r = 0.96), and this was further maintained when comparing the individual parts of the scales (Part I: r = 0.76; Part II: r = 0.92; Part III: r = 0.96; Part IV: r = 0.89). However, it should be noted that no point-by-point conversion algorithm between the MDS-UPDRS and UPDRS is appropriate, due to the changes made in the updated scale.[52] Internal validity was assessed by examining the correlations between different parts of the MDS-UPDRS. The different parts of the MDS-UPDRS were observed to have low correlations with each other (ranging between 0.22 and 0.44), indicating that each part assessed a different aspect of PD. The correlation was slightly higher for parts II and III (r = 0.67), as these covered the objective examinations and patient perceptions of motor function.[52] The authors determined that parts I through III had no floor-to-ceiling effects; however, a floor effect (but no ceiling effect) was observed for Part IV (assessment of the presence and severity of motor complications) of the MDS-UPDRS (lowest = 36.7%).[52]

In an independent cross-sectional, international study by Martinez-Martin et al.[53] that included 435 Spanish-speaking PD patients (comprising all Hoehn & Yahr stages), the MDS-UPDRS was extremely feasible and correlated with global measures of PD disease severity (including Hoehn & Yahr and the Clinical Impression of Severity Index for PD [CISI-PD]) and the PDQ-8 HRQoL measure (Spearman correlation coefficients ranging from 0.36 to 0.89). High correlations between the MDS-UPDRS and the UPDRS were also observed in this study.[53] Convergent validity was apparent between the MDS-UPDRS subscales and other scales (namely the non–motor symptom scale, the rapid assessment of disability scale, and the CISI-PD motor signs and motor complication), which ranged from 0.70 to 0.89.[53]

Internal consistency (using Cronbach alpha) was assessed by Goetz et al. for each of the parts (I through IV) of the MDS-UPDRS.[52] The authors determined there was strong internal consistency for each of the MDS-UPDRS parts: 13 items in Part I (alpha = 0.79), 13 items in Part II (alpha = 0.90), 33 items in Part III (alpha = 0.93), and 6 items in Part IV

(alpha = 0.79). These results were echoed by Martinez-Martin et al.,[53] who examined each part of the MDS-UPDRS and obtained alpha indexes that surpassed 0.70 (parts II and III both surpassed 0.90). The distributions of the total scores between the MDS-UPDRS and the UPDRS were observed to be similar, with a mean of 68.4 (SD of 32.8) and 61.0 (SD of 30.3), respectively, in the Goetz et al. study.[52] In terms of test-retest reliability, Martinez-Martin et al.[53] determined that the intra-class coefficients for all parts of the MDS-UPDRS were greater than 0.90, indicating that the MDS-UPDRS is appropriate for measurements of PD over time.

To determine the MCID for MDS-UPDRS Part III (motor examination), Horvath et al.[26] used a receiver operating characteristic (ROC) analysis for 2 anchor-based methods (a within-patients score-change method and a sensitivity- and specificity-based approach) and a distribution-based method in 728 paired follow-up visits by 260 patients with confirmed PD. The authors determined that the optimal MCID for improvement was 3.25 points and 4.63 points for worsening.[26] Horvath et al.[54] proceeded to determine the MCIDs for Part I (non-motor experiences of daily living) and Part II (motor experiences of daily living), along with a Part I and Part II composite score, using the same ROC analysis for the 2 anchor-based methods and the distribution-based method previously described[26] in 365 patients with PD. The authors calculated the MCID for Part I to be 2.64 points for improvement and 2.45 points for worsening. For Part II, the authors concluded that the MCID threshold was 3.05 points for improvement and 2.51 points for worsening. The MCID thresholds for the composite Part I and Part II score were observed to be 5.73 points for improvement and 4.70 points for worsening.[54] Makkos et al.[55] analyzed 1,312 examinations from 501 PD patients using the PGI-I scale as the anchor and a methodology similar to Horvath et al.[26] and ordinal regression modelling. They determined that the MCID for the MDS-UPDRS Part II and Part III composite was greater than 4.9 points for improvement and less than 4.2 points for worsening. For the composite MDS-UPDRS (sum of Part I, Part II, and Part III), the MCID was 6.7 points for improvement and 5.2 points for worsening. In terms of the total MDS-UPDRS score, the MCID was determined to be 7.1 points for improvement and 6.3 points for worsening.[55] No specific MCID was identified for Part IV of the MDS-UPDRS.

Parkinson's Disease Questionnaire 39

The PDQ-39 is one of the most commonly used PD-specific HRQoL measures. Its measurement properties have been studied extensively and it has been recommended for use by the Movement Disorders Society.[61] The PDQ-39 is a self-administered questionnaire consisting of 39 items that measure 8 domains of health: mobility (10 items), ADL (6 items), emotional well-being (6 items), stigma (4 items), social support (3 items), cognition (4 items), communication (3 items), and bodily discomfort (3 items).[30] Each item is graded on a 5-point Likert scale (0 = never; 4 = always), which are then added to generate the respective domain scores. Each domain is coded on a scale of 0 (no problem at all) to 100 (maximum level of a problem). Further, an overall single summary index, the PDQSI, representing the global HRQoL can be created by averaging the 8 subscale scores. The PDQSI is also coded on a scale ranging from 0 to 100, with higher scores indicating worse quality of life.[30,31]

The psychometric properties of the domain and index score of the PDQ-39 have been extensively evaluated in many studies, across different geographic locations and with different languages. Only the evidence for the English version of the scale is summarized here.

One study by Damiano et al.[32] assessed the comprehensiveness of the PDQ-39 in a clinical trial setting based on a literature review and through consultation with clinicians and patients. The authors found the PDQ-39 measures 10 out of the 12 areas of HRQoL identified as relevant to PD patients, except for self-image and sexual function.[32]

The Damiano et al. study reported the PDQ-39 has a short administration time, estimated to be less than 30 minutes, and can be uniformly administered by the patients, interviewers, or caregivers.[32] One study by Jenkinson et al. validated the PDQ-39 in a cross-culture study across 5 countries (including Canada and the US).[57] Similar to the previous study, a high completion rate (> 82%) and low percentage of missing score (< 5%) was reported for both the domain and index scores.[57] Additionally, assessments of the validity of the PDQ-39 have been conducted in different settings, including clinic-based, community-based, and longitudinal samples, making the interpretation more generalizable.[32]

The UK-based research group that developed the scale assessed the reliability of the PDQ-39 and PDQSI internally with other domain scores and an acceptable internal consistency (Cronbach alpha > 0.7 and > 0.8, respectively) was found, indicating the items performed well enough together to be a composite score. The test-retest reliability (range of 0.68 to 0.94) was high.[30,31] A US study adapted the British version into a US version and found corroborating psychometric properties, with a Cronbach alpha greater than 0.7 for all but 1 domain (social support, alpha = 0.51), and high test-retest reliability (range of 0.86 to 0.95).[62] Similarly, an adequate internal consistency was reported by Damiano et al.[63] (Cronbach alpha ≥ 0.7 across domains and 0.85 for the PDQSI), with the exception of social support (Cronbach alpha = 0.57). Findings from the cross-national validation study were similar, with generally adequate internal consistency for all domains (Cronbach alpha ≥ 0.7), except for social support.

The developers of the PDQ-39 documented the construct (specifically convergent) validity of the individual domain score of the scale in comparison with other patient-reported measures of ill health, namely the Columbia rating scale and Hoehn & Yahr score. While moderate to strong correlations were found between the scales for dimensions measuring physical aspects of health status (mobility and ADL Spearman's correlation, r > 0.5), psychosocial aspects had weak correlations (emotions, stigma, and social: r < 0.3).[57] In contrast, correlations between related PDQ-39 and Short Form-36 (SF-36) domain scores were strong (–0.66 ≤ r ≤ −0.8).[56] The US-based study reported similar findings, with strong correlations between the related PDQ-39 and SF-36 domain scores (−0.59 ≤ r ≤ −0.88), with the exception of the subscale measuring social support (r = −0.22).[62] In addition, the PDQ-39 generally had strong correlations with 5 measures of symptoms severity (tremor, stiffness, slowness, freezing, jerking), as measured by the related SF-36 scales (0.21 ≤ r ≤ 0.74).[62] Concurrent validity in the English version of the PDQ-39 was assessed by Harrison et al. by comparing the performance of PDQ-39 with other established measures of disease severity, depression, and anxiety.[58] The PDQ-39 domains that are related to the Beck depression inventory scores, Barthel index, and the Royal Postgraduate Medical School severity scale had moderate to strong correlations (r ranged from 0.3 to 0.73).[58]

The US-based study assessed the discriminative ability of the PDQ-39 by measuring the scale's ability to discriminate between the stages of PD. Respondents consistently indicated a significantly higher score for each PDQ-39 domain, with progressive worsening of 5 measures of symptom severity (tremor, stiffness, slowness, freezing, jerking).[62] The discriminative ability was further demonstrated by Damiano et al., where higher (poorer)

PDQ-39 domain and index scores were associated with more severe Hoehn & Yahr stages and dyskinesia as well as the presence of comorbidities.[57]

The developers of the PDQ-39 reported moderate responsiveness for 2 of its domains (standardized mean change over time, 0.55 and 0.43 for mobility and ADL, respectively); the responsiveness for the other 6 domains was low.[32] Harrison et al. assessed the comparative responsiveness of the PDQ-39 and other established measures of mood and motor function (the 28-item General Health Questionnaire and the Office of Population and Census Surveys disability instrument) in a UK population.[58] Results from the Harrison et al. study showed the PDQ-39 and its subscales to have superior responsiveness to change over time (except for the domains involving emotion and bodily discomfort). In a naturalistic study (e.g., no intervention, examining patients over time) by Schrag et al., the PDQ-39 showed moderate to significant internal responsiveness in the population-based sample after 1 year in at least 1 measure of the following subscales: social support, communication, and ADL, while after 4 years, internal responsiveness was observed in the communication, ADL, stigma, mobility, and cognition subscales.[33] Additionally, in their clinic-based sample, Schrag et al. observed some change in internal responsiveness at 1 year; however, this was seen only in the summary index, bodily pain, and communication subscales.[33] While the authors did observe internal responsiveness in the PDQ-39 HRQoL scale, they also noted that it was much less than that observed using tools that measured impairment changes, such as Hoehn & Yahr and the UPDRS.[33] In a different study by Tu et al., both the internal and external responsiveness of the PDQ-39 and SF-36 were examined in clinic-based patients with confirmed PD.[34] After a 1-year follow-up, the authors ascertained (using the MDS-UPDRS Part III motor domain) that 16 of 74 patients had improved and 34 had worsened. Significant differences were observed between the baseline and follow-up scores in the PDQ-39 mobility domains in patients who had improved, while significant differences were observed in the summary index score, body discomfort, communication, social support, and emotional well-being scores in patients who worsened.[34] Effect sizes and standardized response means (SRMs) of greater than 0.5 supported moderate to large responsiveness for the PDQ-39 mobility domain (SRM = 0.72) in improved patients and the PDQ-39 social support, PDQSI, and communication (SRM of −0.51, −0.55, and −0.55, respectively) in patients who worsened.[34] The authors determined that the PDQ-39 was responsive to changes in motor difficulties over the year and their findings supported the longitudinal validity of this instrument in patients with PD.[34]

Floor and ceiling effects were evaluated by Damiano et al. on patients with varying degrees of PD severity using a self-completed and telephone-interview version of the PDQ-39. Both modes of administration generally showed low floor and ceiling effects across different domains (range of 0.0% to 6.1% for floor effects and 1.5 to 31.3% for ceiling effects), which was essentially eliminated by the index score. However, the stigma and social support subscale had noticeably higher ceiling effects, indicating a high proportion of study participants had maximum scores for these 2 domains.[63] These findings were consistent with the cross-national validation study,[57] where generally low floor and ceiling effects were seen across different domains (< 15% and 5%, respectively). However, the stigma and social support domain had a large floor effect (> 20% and > 50%, respectively), indicating a substantial proportion of the study participants scored at the floor (i.e., zero); but the floor effect was virtually eliminated by the index score.

The only study examining the scaling assumption in the English version of the PDQ-39 was the cross-national study by Jenkinson et al.[57] The authors reported a higher-order factor analysis to create a single index score, the PDQSI. The index score had eigenvalues

greater than 1 and explained more than 50% of the variance, thus supporting the scaling assumptions.

One study by the original research group that developed the PDQ-39 scale investigated the MCID for the index score as well as across different domains. A postal survey of randomly selected patients from 13 local branches of the Parkinson's Disease Society of the United Kingdom was conducted; the response rate was 53% (N = 728) and no information on PD severity or anchoring was provided. Findings from the study showed a varying mean MCID for different domains: mobility (–3.2), ADL (–4.4), emotional well-being (–4.2), stigma (–5.6), social support (–11.4), cognition (–1.8), communications (–4.2), and pain (–2.1), and –1.6 for the overall score.[35]

Epworth Sleepiness Scale

The ESS is an instrument that examines a patient's sleepiness (or ability to doze off) during the day. There are 8 situations that are assessed:

- sitting and reading
- watching television
- sitting inactively in a public place
- being a passenger in a car for one hour without a break
- lying down to rest in the afternoon when circumstances permit
- sitting and talking to someone
- sitting quietly after lunch without alcohol
- stopping for a few minutes in traffic while driving.[28]

Each item or situation is assigned a score ranging from 0 "would never doze" to 3 "high chance of dozing." A total ESS score is obtained by summing the responses for the 8 individual items, yielding a score between 0 and 24 (with higher scores indicating more sleepiness associated with daily life).

In a cross-sectional study by Hagell and Broman,[28] 118 Swedish-speaking patients with neurologically diagnosed PD were assessed for any sleep-related aspects or fatigue they experienced. Clinical assessments of patients in the ON stage were attained using the UPDRS, Hoehn & Yahr staging, the Schwab and England ADL scale, and the Mini-Mental State Examination, while additional Hoehn & Yahr and Schwab and England ADL scales were administered in the OFF stage. The ESS was then administered to all patients, in addition to the Pittsburgh Sleep Quality Index, in order to ascertain the reliability, floor and ceiling effects, and construct validity of the ESS.[28] The reliability of the ESS was observed to be 0.84 (SD of 0.79 to 0.88) (Cronbach alpha) and there was a marginal floor effect and no ceiling effect.[28] In order to properly assess construct validity, patients were partitioned into 2 groups according to their response to item number 8 of the Pittsburgh Sleep Quality Index: those who did not have any problems staying awake during the past month (n = 81) and those who did have problems staying awake during the past month (n = 30; N = 111 in total). The construct validity of the ESS was supported by a score of 8 (range of 5 to 12) among those patients who did not have problems compared with a score of 14 (range of 7 to 16) in those patients who did have problems staying awake during the past month ($P < 0.0001$ Mann-Whitney U test).[28]

No MCID was identified for the total ESS score in patients with PD.

EuroQol 5-Dimensions 5-Levels Questionnaire

The EQ-5D is a generic quality-of-life instrument developed by the EuroQol Group[36] that can be applied to a wide range of health conditions and treatments.[36] As a generic measure of HRQoL that can capture the net effect of treatment benefits and harms, the EQ-5D provides valuable information from a patient perspective. In addition to this purpose, the EQ-5D is used in clinical trials to obtain utility weights for economic models.[64] The EQ-5D-5L was introduced in 2005 based on the earlier 3-Levels version (EQ-5D-3L).[36] It consists of an EQ-5D descriptive system and the EQ VAS. The descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, each with 5 levels: a level 1 response represents "no problems," level 2 represents "slight problems," level 3 represents "moderate problems," level 4 represents "severe problems," and level 5 represents "extreme problems" or "unable to perform," which is the worst response in the dimension. Respondents are asked to choose the level that reflects their health state for each of the 5 dimensions. In total, there are 3,125 possible unique health states defined by the EQ-5D-5L, with 11111 and 55555 representing the best and worst health states, respectively. The numerical values assigned to levels 1 to 5 for each dimension reflect rank order categories of function. In terms of measurement properties, these are ordinal data; they do not have interval properties and therefore should not be summed or averaged to, for example, produce an individual dimension "score." Results from the EQ-5D-5L descriptive system can be converted into a single index score using a scoring algorithm that takes the local patient and population preferences into account. Therefore, the index score is a country-specific value and a major feature of the EQ-5D instrument.[64]The range of index scores will differ according to the scoring algorithm used; however, in all scoring algorithms for the EQ-5D-5L, a score of 0 represents the health state "dead" and 1.0 reflects "perfect health." Negative scores are also possible for those health states that society (not the individual patient) considers to be "worse than dead."

The EQ VAS records the respondent's self-rated health on a vertical visual analogue scale where the end points are labelled 0 ("the worst health you can imagine") and 100 ("the best health you can imagine"). The respondents are asked to mark an X on the point of the visual analogue scale that best represents their health on that day. The EQ-5D index and EQ VAS scores can be summarized and analyzed as continuous data.[64] Hence, the EQ-5D produces 3 types of data for each respondent:

- a profile indicating the extent of problems on each of the 5 dimensions represented by a 5-digit descriptor, such as 11121 or 21143
- a population preference–weighted health index score based on the descriptive system
- a self-reported assessment of health status based on the EQ VAS.

The EQ-5D-5L has been validated in terms of feasibility, ceiling effects, discriminatory power, and convergent validity in a diverse patient population from 6 countries with chronic conditions.[36] One cross-sectional study of 585 Mexican patients with PD (mean disease duration of 7.6 years; SD of 6.1 years) by Alvarado-Balanos et al. examined the internal consistency of the EQ-5D-5L by comparing it with the disease-specific PDQ-8, which has similar performance to the PDQ-39 but is shorter and easier to complete.[38] The EQ-5D-5L and PDQ-8 index scores were strongly correlated (r_s= −0.75), while all of the individual items between the 2 instruments were moderately correlated (correlations ranging between −0.39 and −0.62).[38] Equivalent domains of the EQ-5D-5L and the PDQ-8 (mobility, ADL and self-care, emotional well-being and anxiety) were strongly correlated (r_s > 0.60) and the EQ

VAS was moderately correlated with both the EQ-5D-5L$_{index}$ and PDQ-8$_{index}$ (r_s of 0.54 and −0.56, respectively).[38] While internal consistency between the 2 scales was observed, agreement between the 2 instruments was not maintained, especially as HRQoL worsened.[38] The authors noted that the ceiling effects previously observed using the EQ-5D-5L were lower in their study and the EQ-5D-5L was observed to perform adequately upon subgroup analyses (age, disease duration, treatment, disease severity, and perceived quality of life); thus indicating that the results could be reproduced in heterogeneous populations.[38] To assess the convergent validity of the EQ-5D-5L in patients with PD, Alvarado-Balanos et al.[38] compared it with the MDS-UPDRS in order to ascertain the Spearman correlation coefficients. In all domains (except for MDS-UPDRS Part IV), the EQ-5D-5L and PDQ-8 index scores were observed to be moderately to strongly correlated with the MDS-UPDRS (r_s ranging between 0.23 and 0.72). Weak to moderate correlations were observed between the EQ VAS and all domains of the MDS-UPDRS (r_s ranging between −0.38 and −0.52). Important limitations of this study include the underrepresentation of patients with Hoehn & Yahr stage 4 to 5 PD, the cross-sectional nature of the study (hence, changes over time were precluded from being analyzed), and the decision to use the version of the EQ-5D-5L that uses a specific disease set from the US (even though there is a large proportion of Mexican inhabitants residing there).[38]

MCID estimates for the index score in the general Canadian population were generated by simulating the effects of single-level transitions in each dimension.[59] The results yielded MCIDs with a summarized mean of 0.056 (SD of 0.011), and a summarized median of 0.056 (interquartile range, 0.049 to 0.063).[59] No MCID specific to PD was identified in the literature.

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