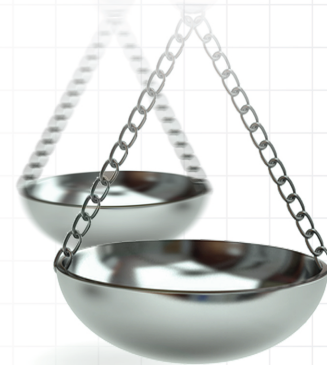




Indirect comparison of apomorphine sublingual film and levodopa inhalation powder for Parkinson's disease 'OFF' episodes

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Aim: To compare efficacy of apomorphine sublingual film (APL) and levodopa inhalation powder (CVT-301) for 'on-demand' treatment of Parkinson's disease 'OFF' episodes. **Patients & methods:** Patient-level data from an APL pivotal study were re-weighted to match average baseline characteristics from a CVT-301 study (SPAN-PD). Placebo-adjusted treatments were compared at week 12. **Results:** Improvements in predose Unified Parkinson's Disease Rating Scale Part III scores were significantly larger for APL versus CVT-301 at 60 min postdose (least squares mean difference-in-difference: -8.82; $p = 0.002$); difference at 30 min favored APL but was not statistically significant (-4.46; $p = 0.103$). Total daily 'OFF' time reductions were significantly larger for APL versus CVT-301 (-1.31 h; $p = 0.013$). **Conclusion:** Results suggest APL treatment may lead to improved efficacy versus CVT-301.

First draft submitted: 23 July 2021; Accepted for publication: 1 December 2021; Published online: 24 January 2022

Keywords: APL-130277 • apomorphine sublingual film • comparative effectiveness • CVT-301 • levodopa inhalation powder • matching-adjusted indirect comparison • motor function • Parkinson's disease • 'OFF' episodes

Parkinson's disease (PD) is a progressive and highly disabling neurologic disorder characterized by both motor (e.g., bradykinesia, postural instability and rigidity or rest tremor) and non-motor symptoms (e.g., cognitive impairment, mood disorders and autonomic dysfunction) [1]. Due to an aging population, the prevalence of PD in the USA is projected to increase from approximately 1 million individuals in 2020 to 1.2 million individuals by 2030 [2].

The administration of levodopa with the dopa decarboxylase inhibitor carbidopa or benserazide compensates for the loss of dopaminergic neurons and is the cornerstone of treatment management for patients with PD (carbidopa/levodopa is approved for use in the USA) [1,3,4]. During the early phase of treatment, carbidopa/levodopa generally provides significant benefits that extend beyond the half-life of levodopa (~1.5 h) [5]. However, motor complications – which include dyskinesia and motor fluctuations – frequently emerge in patients who have been treated with chronic carbidopa/levodopa for ~2 years and are a significant source of impairment for patients [6–8].

Motor fluctuations consist of periods when symptoms improve because of a beneficial response to a carbidopa/levodopa dose ('ON') and periods of suboptimal or variable response to a dose resulting in the reappearance or worsening of motor (e.g., tremor, bradykinesia, rigidity) and non-motor (e.g., cognitive and attention deficits) symptoms (termed 'OFF' episodes) [9]. 'OFF' episodes significantly impact the patient's quality of life [10] and can be managed by adjusting baseline carbidopa/levodopa treatment (i.e., alteration of doses and/or dosing frequency), by adding 'ON-extendors' (i.e., additional maintenance treatments) that extend 'ON' time, or by adding 'on-demand' treatments that are specifically administered during 'OFF' episodes when needed [11]. Initially, subcutaneous apomorphine was the only 'on-demand' treatment specifically approved for 'OFF' episodes in patients with advanced PD [12]. However, despite its effectiveness, this treatment remains underused due to several practical limitations associated with product assembly, mode of administration and skin-related side effects [13].

Two additional treatments address these limitations and are approved by the US FDA for the ‘on-demand’ treatment of ‘OFF’ episodes in patients with PD: levodopa inhalation powder and apomorphine sublingual film [14,15]. To date, no head-to-head randomized controlled trials (RCTs) of these ‘on-demand’ treatments have been conducted to inform treatment decisions, policy decision-making and other healthcare-related issues. Naïve, indirect comparisons may be inappropriate, as the study designs and patient populations might differ extensively. Matching-adjusted indirect comparison (MAIC) analyses used to compare interventions can minimize many biases associated with naïve comparisons between studies by adjusting for differences in patient and study characteristics [16]. MAICs are increasingly being included in submissions to regulators and/or health technology assessment agencies. In this study, MAIC analyses were used to indirectly compare the efficacy of apomorphine sublingual film and levodopa inhalation powder for the ‘on-demand’ treatment of ‘OFF’ episodes in patients with PD.

Methods

Data sources

Data from the apomorphine sublingual film pivotal study [17] were provided by Sunovion Pharmaceuticals Inc. To identify relevant levodopa inhalation powder studies for comparison, a targeted search was conducted in Google, Google Scholar, PubMed and ClinicalTrials.gov. Search terms included ‘Inbrija,’ ‘levodopa inhalation powder,’ ‘trial’ and ‘efficacy,’ and phase III and IV studies were considered. Three studies for levodopa inhalation powder [18–20] were retrieved. After assessing cross-study similarities and differences, two levodopa inhalation powder studies were excluded because they were open-label [18,19]. Only the SPAN-PD study was deemed comparable with the apomorphine sublingual film pivotal study in terms of design and selection criteria.

The apomorphine sublingual film pivotal study was a phase III, randomized, multicenter, double-blind, placebo-controlled study that enrolled patients 18 years of age or older with a diagnosis of PD [17]. Patients were randomized to receive either apomorphine sublingual film (10–35 mg) or placebo. The primary end point was the change from predose to 30 min postdose in the Movement Disorder Society Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) Part III score at week 12 obtained in the clinic; this end point was also evaluated at 15, 45, 60 and 90 min postdose. In addition, study drug administrations per day were recorded via patients’ home-dosing and response diaries during the 2 days preceding each clinic maintenance visit. The SPAN-PD study was a phase III, randomized, multicenter, double-blind, placebo-controlled study that enrolled patients aged 30–85 years of age with a diagnosis of PD [20]. Patients were randomized to receive levodopa inhalation powder 60 mg or 84 mg, or placebo. Only data for the 84-mg arm were used in the current study, as this is the recommended dose per the prescribing information [14]. The primary end point was the change in the Unified Parkinson’s Disease Rating Scale (UPDRS) Part III score from predose to 30 min postdose assessed at week 12 during an in-clinic ‘OFF’ episode; additional timepoints were also evaluated postdose (i.e., 10, 20 and 60 min). The study evaluated total daily ‘OFF’ time at week 12 using patient diary data completed at home in the 3 days before a scheduled clinic visit.

Study measures & end points

Baseline characteristics reported consistently in both studies included demographics (i.e., age, sex and race), body mass index, Mini-Mental State Examination total score, time since PD diagnosis, modified Hoehn and Yahr stage, smoking history, daily levodopa dose, number of ‘OFF’ episodes per day, total time of ‘OFF’ episodes per day, dyskinesia, and use of other drugs for PD. In addition, UPDRS Part III score at screening could be compared after imputation. Specifically, because the apomorphine sublingual film pivotal study used the MDS-UPDRS (instead of the UPDRS, which was used in SPAN-PD), 7 points were subtracted from the raw MDS-UPDRS scores to allow for comparison with SPAN-PD [21].

The primary end point for the MAIC analyses was the mean change in the UPDRS Part III score at week 12 from predose to the following timepoints postdose: 15 (apomorphine sublingual film pivotal study) or 20 (SPAN-PD), 30 and 60 min.

The secondary end point was the reduction in total daily ‘OFF’ time at week 12; methods for the collection and reporting of this end point are described separately for each ‘on-demand’ treatment.

Levodopa inhalation powder

In the SPAN-PD study, enrollees could be ‘ON’ at the start of their clinical visit, and the study investigators observed when patients transitioned to ‘OFF’ before administering levodopa inhalation powder [20]. Patients were

considered to have achieved 'ON' if medication was providing benefit with respect to mobility, slowness, and stiffness, and may or may not be providing complete alleviation of all PD symptoms.

The secondary end point was evaluated by SPAN-PD study investigators using home diary data entered by patients during the 3 days preceding a clinic visit [20]. Patients recorded whether they were predominantly 'OFF' or 'ON' during waking hours at intervals of 30 min [20]. For this MAIC, the value for reduction in total daily of 'OFF' time for the 84-mg dose of levodopa inhalation powder versus placebo was derived directly from the SPAN-PD primary publication (-0.01 h) [20].

Apomorphine sublingual film

Unlike enrollees in the SPAN-PD study, enrollees in the apomorphine sublingual film pivotal study were required to have withheld their antiparkinsonian medication for 12 h overnight before their visit and were therefore in practically defined 'OFF' before receiving apomorphine sublingual film [17]. Patients were considered to be 'ON' if they achieved a FULL 'ON,' defined as a period of time where apomorphine sublingual film provided benefit with regard to mobility, stiffness and slowness, the patient had adequate motor function to perform normal daily activities, and patient-assessed response was comparable to or better than normal response to PD medications before enrolling in the study.

As the apomorphine sublingual film pivotal study did not directly report reduction in total daily 'OFF' time at week 12, it was derived from individual patient data (IPD) by multiplying the mean number of apomorphine sublingual film treatments per day and the imputed duration of FULL 'ON' per treatment episode.

Mean reduction in 'OFF' hours per day =

mean number of treated episodes per day $\times$ mean duration of FULL 'ON' per episode due to therapy

The mean number of apomorphine sublingual film treatments per day was calculated from the patients' home dosing and response diary data recorded during the 2 days before each clinic visit in the pivotal study. Missing diary data from patients in the apomorphine sublingual film pivotal study were assigned the mean of the non-missing data for each study arm (apomorphine sublingual film and placebo). The duration of FULL 'ON' per treatment episode was estimated using in-clinic data on patients' FULL 'ON'/'OFF' status at discrete timepoints (15, 30, 45, 60 and 90 min postdose) in the double-blind maintenance phase of the apomorphine sublingual film pivotal study, given a set of assumptions. First, if two consecutive discrete timepoints reported different results for FULL 'ON'/'OFF,' then the patient was assumed to have changed status exactly midway between the timepoints. For example, a patient who was 'OFF' at 15 min and had a FULL 'ON' at 30 min was assumed to have entered FULL 'ON' midway at 22.5 min. Second, patients who were still FULL 'ON' at the last timepoint measured (i.e., 90 min) were assumed to remain FULL 'ON' until 105 min (aligning with the 15-min midpoint between the previous 60- and 90-min timepoints). Third, nonresponders who did not turn FULL 'ON' during the 90-minute observation window were assumed to experience 0 min of FULL 'ON' time per treatment episode.

Statistical analysis

Matching-adjusted indirect comparison

Details on the MAIC methodology were previously published [16]. A subset of patients from the apomorphine sublingual film pivotal study were selected for analysis using the eligibility criteria of SPAN-PD to later compare similar populations (Table 1). The MAIC approach used IPD from the apomorphine sublingual film pivotal study and adjusted the study population to match the average baseline characteristics reported for SPAN-PD. Prior to matching, unadjusted baseline characteristics were compared across studies between the two pooled samples (i.e., the active treatment and placebo arms) using Wald tests for continuous variables and chi-square tests (or the Fisher exact test for expected counts <5) for categorical variables. Baseline characteristics that significantly differed between studies or served as clinically meaningful effect modifiers were matched to account for possible differences at baseline across the apomorphine sublingual film pivotal study and SPAN-PD.

Individual patients in the apomorphine sublingual film pivotal study were assigned weights such that weighted means and proportions for baseline characteristics in the pooled sample exactly matched those reported for the pooled SPAN-PD population, and the weighting was equal to the patient's estimated odds of enrolling in SPAN-PD versus the apomorphine sublingual film pivotal study. Weights were derived using a logistic regression model

Table 1. Selection of patients from the apomorphine sublingual film pivotal study based on the eligibility criteria of SPAN-PD[†].

Step	Description	n	% of total	% of previous
1	All patients with non-missing matching characteristics	108	100	100
2	Age: between 30 and 85 years	108	100	100
3	Modified Hoehn and Yahr stage when 'ON': between 1 and 3	108	100	100
4	Total 'OFF' time per day: ≥ 2 h	108	100	100
5	Daily levodopa dose: 1600 mg/day or less	96	89	89
6	Carbidopa/levodopa responders ($\geq 25\%$ UPDRS improvement) [‡]	96	89	100
7	MMSE total score ≥ 25	96	89	100
8	Exclude orthostatic hypotension in medical history	90	83	94
9	Exclude chronic respiratory disease in medical history [§]	82	76	91
10	Exclude severe dyskinesia at screening [¶]	81	75	99

[†]Measures of lung function (ability to do spirometry, FEV₁ and FEV₁ to FVC ratio) used in the SPAN-PD study were not assessed in the apomorphine sublingual film pivotal study. This is unlikely to have a large impact on the comparison.

[‡]To identify carbidopa/levodopa responders during screening, the SPAN-PD study required $\geq 25\%$ improvement in UPDRS score from predose to postdose. This was derived in the IPD from the apomorphine sublingual film pivotal study at screening visit 2.

[§]In the SPAN-PD study, patients with chronic respiratory disease in the past 5 years were excluded. For comparability, patients in the apomorphine sublingual film pivotal study with asthma or chronic obstructive pulmonary disease in their medical history were excluded.

[¶]The SPAN-PD study excluded patients with dyskinesia severe enough to "interfere with their ability to participate or perform study procedures." In the IPD from the apomorphine sublingual film pivotal study, patients with severe dyskinesia at screening visit 2 were identified as those who responded that the functional impact of dyskinesia was "severe" (level 4) in question 4.2 of the MDS-UPDRS questionnaire.

FEV: Forced expiratory volume; FVC: Forced vital capacity; IPD: Individual patient data; MDS-UPDRS: Movement Disorder Society Unified Parkinson's Disease Rating Scale; MMSE: Mini-Mental State Examination; PD: Parkinson's disease; UPDRS: Unified Parkinson's Disease Rating Scale.

estimating the propensity of a patient to enroll in SPAN-PD versus the apomorphine sublingual film pivotal study, with the following baseline characteristics as covariates: modified Hoehn and Yahr stage < 2.5 , UPDRS Part III score at screening while 'OFF,' baseline dyskinesia, and number of 'OFF' episodes per day. Between the two variables related to daily 'OFF' episodes (i.e., number of 'OFF' episodes vs. total daily 'OFF' time), only one was included in the model. The cross-study comparison of these two variables differed in direction, possibly due to differences in how these variables were collected or calculated. The number of daily 'OFF' episodes was included in the model, as clinical experts suggested that patients understood and reported this measure more reliably than total daily 'OFF' time. After matching, baseline characteristics were compared using Wald tests.

Efficacy end points

Consistent with the SPAN-PD study, each efficacy end point was assessed using a Mixed Model for Repeated Measures (MMRM) analysis. The model for each end point was fitted using IPD from the apomorphine sublingual film pivotal study and included treatment group, visit, modified Hoehn and Yahr stage, and treatment-by-visit interaction as fixed effects. Additionally, for change from predose in UPDRS Part III score (the primary end point), the model adjusted for UPDRS Part III score at baseline while 'OFF.' For reduction in total daily 'OFF' time (the secondary end point), the model adjusted for daily 'OFF' time at baseline. The SPAN-PD models, however, also included lung function at screening, as measured by the forced expiratory volume in 1 s to forced vital capacity ratio. Because this measure was not relevant or available in the apomorphine sublingual film pivotal study and was not expected to impact the efficacy of apomorphine sublingual film, it was left out of the MMRM developed using IPD from this study.

Before and after matching, the primary and secondary end points were compared between studies based on the difference between the effects of the active arm and the placebo arm (i.e., the difference-in-difference method). End points were compared using Wald tests.

Results

After applying the SPAN-PD eligibility criteria, 44 patients assigned to the treatment arm from the apomorphine sublingual film pivotal study and 37 patients assigned to the placebo arm were included in the comparison (Table 1). The baseline characteristics and outcomes of these patients were compared with the 114 patients assigned to the treatment arm of SPAN-PD and the 112 patients assigned to the placebo arm of SPAN-PD.

Table 2. Unadjusted baseline characteristics of patients from the apomorphine sublingual film pivotal study and SPAN-PD.

	Apomorphine sublingual film pivotal study			SPAN-PD			p-value [†]
	Treatment (n = 44)	Placebo (n = 37)	Overall (n = 81)	Treatment (n = 114)	Placebo (n = 112)	Overall (n = 226)	
Age (years)	63.30 ± 9.57	61.27 ± 8.46	62.37 ± 9.08	63.50 ± 7.97	62.60 ± 8.83	63.05 ± 8.42	0.6
Male, n (%)	28 (64)	21 (57)	49 (60)	83 (73)	86 (77)	169 (75)	<0.05
Race, n (%)							
White	41 (93)	35 (95)	76 (94)	107 (94)	107 (96)	214 (95)	1
Black	0	1 (3)	1 (1)	4 (4)	0	4 (2)	1
Asian	3 (7)	1 (3)	4 (5)	2 (2)	4 (4)	6 (3)	0.3
BMI (kg/m ²)	27.25 ± 5.25	30.30 ± 6.44	28.64 ± 5.98	27.43 ± 4.66	27.63 ± 5.33	27.53 ± 5.00	0.1
MMSE total score	28.9 ± 1.4	28.9 ± 1.2	28.9 ± 1.3	29.0 ± 1.3	28.8 ± 1.5	28.9 ± 1.4	1
Time since PD diagnosis (months)	105.5 ± 52.0	111.2 ± 38.3	108.1 ± 46.1	95.7 ± 46.3	97.4 ± 54.1	96.5 ± 50.3	0.1
Disease severity, n (%)							
Modified Hoehn and Yahr stage <2.5	34 (77)	30 (81)	64 (79)	72 (63)	74 (66)	146 (65)	<0.05
Modified Hoehn and Yahr stage ≥2.5	10 (23)	7 (19)	17 (21)	42 (37)	38 (34)	80 (35)	<0.05
Smoking history, n (%)							
Never smoked	27 (61)	26 (70)	53 (65)	65 (57)	72 (64)	137 (61)	0.5
Former smoker	14 (32)	10 (27)	24 (30)	44 (39)	37 (33)	81 (36)	0.4
Current smoker	3 (7)	1 (3)	4 (5)	5 (4)	3 (3)	8 (4)	0.5
Daily levodopa dose (mg/day)	897.2 ± 331.1	865.7 ± 316.4	882.8 ± 322.8	818.6 ± 401.0	841.4 ± 396.5	829.9 ± 398.9	0.2
UPDRS Part III score at screening [‡]							
'OFF' episode	35.7 ± 14.3	37.2 ± 14.6	36.4 ± 14.4	33.0 ± 11.0	35.4 ± 12.4	34.2 ± 11.8	0.2
'ON'	10.2 ± 7.9	11.1 ± 9.4	10.6 ± 8.6	14.9 ± 7.4	16.1 ± 8.3	15.5 ± 7.9	<0.001
'OFF' episodes							
Number of 'OFF' episodes per day	3.95 ± 1.20	3.62 ± 1.30	3.80 ± 1.25	3.58 ± 1.09	3.28 ± 1.10	3.43 ± 1.11	<0.05
Total 'OFF' time per day (h) [§]	3.71 ± 1.63	3.80 ± 1.53	3.75 ± 1.58	5.35 ± 2.26	5.59 ± 2.25	5.47 ± 2.26	<0.001
Patients with dyskinesia before baseline, n (%)	26 (59)	26 (70)	52 (64)	53 (46)	46 (41)	99 (44)	<0.01
Other Parkinson's disease drug use, n (%)							
Dopamine agonists	25 (57)	22 (59)	47 (58)	69 (61)	61 (54)	130 (58)	1
MAO-B inhibitor	19 (43)	18 (49)	37 (46)	45 (39)	43 (38)	88 (39)	0.4
COMT inhibitor	3 (7)	5 (14)	8 (10)	17 (15)	15 (13)	32 (14)	0.4
Amantadine	8 (18)	10 (27)	18 (22)	23 (20)	22 (20)	45 (20)	0.8

Means and standard deviations are shown for continuous characteristics; counts and percentages are shown for categorical characteristics.

[†] Overall pooled samples (i.e., active treatment and placebo arms) were compared across studies. p-values for continuous variables were calculated using the Wald test. p-values for categorical variables were calculated using the chi-square test. The Fisher exact test was used for categorical variables with small frequency (i.e., n < 5).

[‡] For comparability to SPAN-PD, MDS-UPDRS scores from the apomorphine sublingual film pivotal study were converted to UPDRS scores and reported at screening visit 2. Note that the published value from the apomorphine sublingual film pivotal study was measured at the baseline visit (last titration visit), not at screening visit 2. UPDRS Part III score during 'ON' information was non-missing for 43 patients treated with apomorphine sublingual film and 36 patients who received placebo in the apomorphine sublingual film pivotal study, and 113 patients who received levodopa inhalation powder from SPAN-PD.

[§] Total 'OFF' time per day in the apomorphine sublingual film pivotal study was derived from the number of 'OFF' episodes per day and the typical length of an 'OFF' episode reported by patients.

BMI: Body mass index; COMT: Catechol-O-methyltransferase; MAO-B: Monoamine oxidase-B; MDS-UPDRS: Movement Disorder Society Unified Parkinson's Disease Rating Scale; MMSE: Mini-Mental State Examination; PD: Parkinson's disease; UPDRS: Unified Parkinson's Disease Rating Scale.

Baseline characteristics

Prior to matching, there were significant differences in baseline characteristics between the pooled samples from both studies (Table 2). The SPAN-PD study had a significantly larger proportion of male patients compared with the apomorphine sublingual film pivotal study (75 vs. 60%; p < 0.05). Patients in SPAN-PD experienced more severe PD, according to their modified Hoehn and Yahr stage (proportion ≥2.5: 35 vs. 21%; p < 0.05), UPDRS Part III score while 'ON' (mean 15.5 vs. 10.6 points; p < 0.001), and total 'OFF' time per day (mean 5.47 vs. 3.75 h; p < 0.001). Notably, however, patients from the apomorphine sublingual film pivotal study were significantly more likely to have had dyskinesia before baseline (64 vs. 44%; p < 0.01) and had more 'OFF' episodes per day at baseline (mean 3.80 vs. 3.43; p < 0.05).

Table 3. Adjusted baseline characteristics of patients from the apomorphine sublingual film pivotal study and SPAN-PD.

	Apomorphine sublingual film pivotal study			SPAN-PD			p-value [†]
	Treatment (n = 44)	Placebo (n = 37)	Overall (n = 81)	Treatment (n = 114)	Placebo (n = 112)	Overall (n = 226)	
Age (years)	62.95 ± 9.16	60.93 ± 8.31	62.04 ± 8.79	63.50 ± 7.97	62.60 ± 8.83	63.05 ± 8.42	0.4
Male, %	64	57	61	73	77	75	0.1
Race, %							
White	93	95	94	94	96	95	0.8
Black	0	3	1	4	0	2	0.7
Asian	7	2	5	2	4	3	0.4
BMI (kg/m ²)	27.27 ± 4.75	29.78 ± 5.97	28.40 ± 5.45	27.43 ± 4.66	27.63 ± 5.33	27.53 ± 5.00	0.2
MMSE total score	28.8 ± 1.5	29.0 ± 1.2	28.9 ± 1.3	29.0 ± 1.3	28.8 ± 1.5	28.9 ± 1.4	1
Time since PD diagnosis (months)	96.1 ± 51.4	104.3 ± 36.9	99.8 ± 45.4	95.7 ± 46.3	97.4 ± 54.1	96.5 ± 50.3	0.6
Disease severity, %							
Modified Hoehn and Yahr stage <2.5 [‡]	62	68	65	63	66	65	~
Modified Hoehn and Yahr stage ≥2.5	38	32	35	37	34	35	1
Smoking history, %							
Never smoked	61	72	66	57	64	61	0.4
Former smoker	35	27	32	39	33	36	0.5
Current smoker	3	1	2	4	3	4	0.5
Daily levodopa dose (mg/day)	848.9 ± 312.2	867.4 ± 294.1	857.2 ± 302.4	818.6 ± 401.0	841.4 ± 396.5	829.9 ± 398.9	0.5
UPDRS Part III score at screening [§]							
‘OFF’ episode [‡]	33.2 ± 13.4	35.4 ± 14.0	34.2 ± 13.6	33.0 ± 11.0	35.4 ± 12.4	34.2 ± 11.8	~
‘ON’	8.5 ± 7.8	9.8 ± 8.8	9.1 ± 8.2	14.9 ± 7.4	16.1 ± 8.3	15.5 ± 7.9	<0.001
‘OFF’ episodes							
Number of ‘OFF’ episodes per day [‡]	3.62 ± 0.99	3.20 ± 1.21	3.43 ± 1.11	3.58 ± 1.09	3.28 ± 1.10	3.43 ± 1.11	~
Total ‘OFF’ time per day (h) [¶]	4.04 ± 1.88	3.51 ± 1.41	3.80 ± 1.70	5.35 ± 2.26	5.59 ± 2.25	5.47 ± 2.26	<0.001
Patients with dyskinesia before baseline [‡] , %	37	53	44	46	41	44	~
Other Parkinson’s disease drug use, %							
Dopamine agonists	53	71	61	61	54	58	0.6
MAO-B inhibitor	38	43	41	39	38	39	0.8
COMT inhibitor	5	13	9	15	13	14	0.2
Amantadine	15	26	20	20	20	20	1

Means and standard deviations are shown for continuous characteristics; counts and percentages are shown for categorical characteristics.

[†] Overall pooled samples (i.e., active treatment and placebo arms) were compared across studies. p-values were calculated using the Wald test. The p-value was not calculated for variables that were matched on.

[‡] Variable was included in the propensity score model used for matching. Continuous variables were matched on mean, and categorical variables were matched on proportion. Treatment and placebo arms were pooled to generate the weights.

[§] For comparability to SPAN-PD, apomorphine sublingual film pivotal study MDS-UPDRS scores were converted to UPDRS scores and reported at screening visit 2. Note that the published value for the apomorphine sublingual film pivotal study in Olanow *et al.* was measured at the baseline visit (last titration visit), not at screening visit 2. UPDRS Part III score during ‘ON’ information was non-missing for 43 patients treated with apomorphine sublingual film and 36 patients who received placebo in the apomorphine sublingual film pivotal study, and 113 patients who received levodopa inhalation powder.

[¶] Total ‘OFF’ time per day in the apomorphine sublingual film pivotal study was derived from the number of ‘OFF’ episodes per day and the typical length of an ‘OFF’ episode reported by patients.

BMI: Body mass index; COMT: Catechol-O-methyltransferase; MAO-B: Monoamine oxidase-B; MDS-UPDRS: Movement Disorder Society Unified Parkinson’s Disease Rating Scale; MMSE: Mini-Mental State Examination; PD: Parkinson’s disease; UPDRS: Unified Parkinson’s Disease Rating Scale.

After matching, most baseline characteristics were adequately balanced between the pooled study populations (Table 3). However, patients in the apomorphine sublingual film pivotal study had significantly lower mean UPDRS Part III scores while ‘ON’ (9.1 vs. 15.5) and mean total baseline daily ‘OFF’ times (3.80 vs. 5.47 h) compared with patients in the SPAN-PD study (all $p < 0.001$).

Table 4. Comparison of efficacy end points at week 12 between patients from the apomorphine sublingual film pivotal study and SPAN-PD.

	Before matching				After matching			
	Apomorphine sublingual film pivotal study (n = 81)	SPAN-PD (n = 226)	Difference-in-difference (95% CI)	p-value [†]	Apomorphine sublingual film pivotal study (n = 81)	SPAN-PD (n = 226)	Difference-in-difference (95% CI)	p-value [†]
Change from predose UPDRS Part III score, LS mean difference ^{‡,§}								
15–20 min postdose [¶]	-1.98	-2.55	0.57 (-4.33, 5.48)	0.818	-2.40	-2.55	0.15 (-4.72, 5.02)	0.953
30 min postdose	-6.78	-3.92	-2.86 (-8.46, 2.73)	0.316	-8.38	-3.92	-4.46 (-9.83, 0.9)	0.103
60 min postdose	-12.46	-4.90	-7.55 (-13.39, -1.72)	0.011	-13.72	-4.90	-8.82 (-14.28, -3.35)	0.002
Reduction in total daily 'OFF' time (h), LS mean difference ^{‡,¶}	-0.93	-0.01	-0.92 (-1.80, -0.04)	0.040	-1.32	-0.01	-1.31 (-2.35, -0.27)	0.013

[†]p-values were calculated using the Wald test.

[‡]For a particular study, LS mean difference between active treatment and placebo arms was reported. For comparison across studies, the 'difference-in-difference' between the apomorphine sublingual film pivotal study and SPAN-PD was reported.

[§]At week 12, change from predose UPDRS Part III score was assessed using a MMRM analysis as specified in the SPAN-PD study. This model included treatment group, visit, modified Hoehn and Yahr stage, and treatment-by-visit interaction as fixed effects, adjusting for 'OFF' episode baseline UPDRS Part III score.

[¶]The 15-min postdose timepoint from the apomorphine sublingual film pivotal study was compared with the 20-min postdose timepoint from SPAN-PD.

[¶]To calculate reduction in total daily 'OFF' time in the apomorphine sublingual film pivotal study, the imputed duration of 'ON' per treatment episode at each visit was multiplied by the mean number of treatments per day, as recorded in the patient diary data for a given visit.

APL: Apomorphine sublingual film; LS: Least squares; MDS-UPDRS: Movement Disorder Society Unified Parkinson's Disease Rating Scale; MMRM: Mixed Model for Repeated Measures; UPDRS: Unified Parkinson's Disease Rating Scale.

Efficacy end points

The unmatched and matched placebo-adjusted efficacy end points by treatment arms are shown in Table 4. The results described here are the least squares (LS) mean difference-in-difference after matching.

In the matched populations, the placebo-adjusted change from predose UPDRS Part III score at week 12 (primary end point) was not significantly different between apomorphine sublingual film and levodopa inhalation powder at 15–20 min postdose (LS mean difference-in-difference [95% confidence interval (CI)]: 0.15 [-4.72, 5.02]), but a numerical trend that favored apomorphine sublingual film was observed at 30 min postdose (-4.46 [-9.83, 0.90]; all $p > 0.05$; Table 4). At 60 min postdose, there was a statistically significant difference in favor of apomorphine sublingual film (-8.82 [-14.28, -3.35]; $p = 0.002$). For the secondary end point, placebo-adjusted reductions in daily 'OFF' time at week 12 were significantly larger with apomorphine sublingual film than with levodopa inhalation powder (-1.31 h [-2.35, -0.27]; $p = 0.013$). Similar trends were observed in the analysis of the unmatched populations.

Discussion

In this study, the efficacy of apomorphine sublingual film and levodopa inhalation powder was compared using MAIC, a statistical technique that reweights the sample of one study (with IPD available) to account for differences in study populations. After matching, all placebo-adjusted efficacy end points (change from predose UPDRS Part III score and reduction in total daily 'OFF' time) were numerically improved for patients treated with apomorphine sublingual film, and results before and after matching yielded the same conclusions.

Results for the primary end point of this MAIC suggest that patients treated with apomorphine sublingual film experienced comparable reductions in predose UPDRS Part III score versus levodopa inhalation powder at the earliest postdose timepoint and greater reductions at 30 min postdose and beyond, with the difference-in-difference between treatments being significant in favor of apomorphine sublingual film at 60 min postdose. A numerical treatment difference in favor of levodopa inhalation powder was observed at 15–20 min postdose but was marginal and not statistically significant. Notably, for this earliest timepoint, data were collected at 15 min postdose for apomorphine sublingual film and compared with data collected at 20 min postdose for levodopa inhalation powder, owing to differences in respective study designs. Since apomorphine sublingual film had 5 min less time to establish therapeutic benefit, it is possible that its measured efficacy would have been improved if data were available at 20 min postdose. Consistent with the primary end point, results for reduction in total daily 'OFF' time (secondary end point) also showed that apomorphine sublingual film was associated with significantly greater improvement compared with levodopa inhalation powder.

The statistically significant difference in predose UPDRS Part III score observed at 60 min postdose in favor of apomorphine sublingual film compared with levodopa inhalation powder is likely to be clinically relevant. Shulman *et al.* estimated the minimal clinically important difference (CID) on the UPDRS Part III score to be 2.3 to 2.7 points, a moderate CID to be 4.5 to 6.7 points, and a large CID to be 10.7 to 10.8 points [22]. Based on these estimates, the difference between apomorphine sublingual film and levodopa inhalation powder (-8.8 points) observed at 60 min postdose would qualify as a moderate-to-large difference in terms of clinical significance. However, it should be noted that these ‘on-demand’ treatments are not stand-alone and are typically utilized in conjunction with maintenance carbidopa/levodopa. Mechanisms that explain the difference in clinical effect observed are unclear. Both ‘on-demand’ treatments are designed to act rapidly and bypass first-pass metabolism, and both treatments have clinical trial data to support these attributes [17,20]. At present, there is a knowledge gap in the comparative efficacy of available ‘on-demand’ treatments for patients with PD. Results from this study will help in paving the way for future RCTs and real-world studies to fill the knowledge gap. The extent that patient satisfaction or ease of administration may play a role on clinical effect is also not clear. A recently published patient preference study demonstrated that patients preferred a theoretical dissolvable sublingual film to a theoretical inhaled medication [23].

In the absence of head-to-head RCTs, indirect comparisons are useful to inform the comparative efficacy of two treatments. However, even when anchored to the same comparator treatment (e.g., placebo), indirect comparisons of aggregate data can be prone to biases due to cross-study differences in patient populations or study designs. In the current MAIC analysis, the comparison of unadjusted patient characteristics shows that the SPAN-PD population included more male patients, patients with more severe disease at baseline (as measured by Hoehn and Yahr stage), and fewer patients with dyskinesia compared with patients in the apomorphine sublingual film pivotal study. Without proper adjustments, these differences may introduce bias and confound the analysis of efficacy outcomes. By combining IPD from one study and aggregate data from a comparator study, MAIC addresses such limitations and provides more reliable estimates [16].

After matching, baseline characteristics were largely balanced between the studies, with two exceptions. UPDRS Part III score during ‘ON’ status and total daily ‘OFF’ time remained significantly lower for the pooled sample from the apomorphine sublingual film pivotal study compared with the pooled SPAN-PD population. These two characteristics were defined and calculated differently between studies (limitations detailed below). Therefore, the post-matching difference between study populations may be partially attributable to these methodological issues, rather than to clinically meaningful differences that may confound the results.

Limitations

The present results must be interpreted in light of certain limitations. First, indirect comparisons can be biased by observed and unobserved cross-study differences. However, applying the eligibility criteria of SPAN-PD to the population from the apomorphine sublingual film pivotal study and the use of propensity score-based matching should mitigate the potential impact of these limitations. Second, the SPAN-PD study and the apomorphine sublingual film pivotal study used different scales (i.e., UPDRS vs. MDS-UPDRS, respectively) to assess the primary end point [17,20]. For this reason, 7 points were subtracted from the MDS-UPDRS scores recorded in IPD from the apomorphine sublingual film pivotal study, as recommended by a validated method [21]; this should mitigate the impact of this limitation. Third, reduction in total daily ‘OFF’ time was reported in the SPAN-PD study using patient diary data, whereas this end point was not directly reported in the apomorphine sublingual film pivotal study and was therefore derived using a combination of in-clinic data and outpatient diary data [17,20]. The assumptions that underlie this calculation and the different settings of measurement (i.e., in-clinic vs. home dosing and response diary data) may affect the comparability of this end point between both studies. Fourth, the earliest timepoint for the apomorphine sublingual film pivotal study was 15 min postdose and for the SPAN-PD study it was 10 min postdose [17,20]. To allow for a more conservative comparison, a 20-min timepoint was used for the SPAN-PD study.

The definitions of predose ‘OFF’ and postdose ‘ON’ used in the apomorphine sublingual film pivotal study may have been more stringent than those used in the SPAN-PD study. Enrollees in the apomorphine sublingual film pivotal study were required to have withheld their antiparkinsonian medication for 12 h overnight before their visit and were therefore in practically defined ‘OFF’ [17]. In contrast, SPAN-PD enrollees could be ‘ON’ at the start of their visit, and the study investigators would observe when patients transitioned to ‘OFF’ before administering the study drug [20]. For postdose ‘ON,’ the apomorphine sublingual film pivotal study required that

patients achieved FULL 'ON' [17]. Though the SPAN-PD study did not specify the type of 'ON' [20], the pooled SPAN-PD population did report significantly worse UPDRS Part III scores while 'ON' at screening relative to the pooled sample from the apomorphine sublingual film pivotal study, even after matching, which suggests that the SPAN-PD study may have had a lower threshold for what qualified as 'ON.' Because of these methodological differences, the improvements noted in the SPAN-PD study may be less pronounced than those observed for the apomorphine sublingual film pivotal study.

Conventional patient diary data were used as the source for 'OFF' and 'ON' data in both studies included in this treatment comparison. As the concept of 'OFF' and 'ON' is subjective and may vary from patient to patient, newer automated methods for collecting objective 'OFF' and 'ON' data have been discussed and recommended [24]. Recent advances in technology have opened the possibility to develop an easy-to-use and patient-friendly electronic diary or tracker that allows for continuous monitoring and feedback on day-to-day functioning [24]. Such a tool could help to redefine the use of diaries for the collection of 'OFF' and 'ON' time in clinical trials and produce more refined estimates for efficacy end points such as the reduction in 'OFF' time.

Although our data suggest that apomorphine sublingual film treatment may lead to improved efficacy compared with levodopa inhalation powder, we do not report data on adverse events. Adverse events observed in clinical trials may affect treatment selection for the 'on-demand' treatment of 'OFF' episodes in patients with PD. Apomorphine sublingual film use may be limited by oral/pharyngeal soft tissue swelling, pain and paresthesia [15], whereas cough and upper respiratory tract infections may limit the use of levodopa inhalation powder [14].

Conclusion

This was the first study, to our knowledge, to examine the comparative efficacy of apomorphine sublingual film and levodopa inhalation powder for the 'on-demand' treatment of 'OFF' episodes in patients with PD. While direct comparisons in head-to-head RCTs are considered the 'gold standard,' this placebo-anchored MAIC enabled a timely and statistically robust comparison of the efficacy of apomorphine sublingual film and levodopa inhalation powder. The results suggest that patients who received apomorphine sublingual film experienced significantly greater improvements in motor function 60 min postdose and a significantly greater reduction in total daily 'OFF' time compared with patients who received levodopa inhalation powder. These findings may prove useful to assist physicians in the selection of the most appropriate 'on-demand' treatment for 'OFF' episodes in patients with PD.

Author contributions

All authors contributed to the conception or design of the work. MLZ, NK, KY and KG performed the data analysis and drafted the manuscript. All authors interpreted the results and critically revised the present manuscript for important intellectual content. All authors approve the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Financial & competing interests disclosure

This study was supported by funding from Sunovion Pharmaceuticals Inc. (Marlborough, MA, USA). A Thach, E Pappert, D Mehta and GR Williams are employees of Sunovion Pharmaceuticals Inc. ML Zichlin, N Kirson, K Yang and K Gaburo are employees of Analysis Group, Inc. (Boston, MA, USA), which has received consulting fees from Sunovion Pharmaceuticals Inc. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Medical writing and editorial assistance were provided by S Rochette, an employee of Analysis Group, Inc., and R Schupp and E Thrower of The Lockwood Group (Stamford, CT, USA). Support for this assistance was provided by Sunovion Pharmaceuticals Inc.

Ethical conduct of research

This study was a matching-adjusted indirect comparison of clinical trial data from two published studies. The original trials from the two published studies were conducted in accordance with the Declaration of Helsinki, International Conference on Harmonization Good Clinical Practice guidelines, institutional review boards at participating institutions approved the study protocols and amendments, and all patients provided written informed consent. There were no interactions with human subjects in this matching-adjusted indirect comparison.

Data sharing statement

Data for this study will be made available upon request via the Clinical Study Data Request site (<http://clinicalstudydatarequest.com>).

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Summary points

Background

- To date, no head-to-head studies have compared the efficacy of apomorphine sublingual film and levodopa inhalation powder (CVT-301) as ‘on-demand’ treatments for ‘OFF’ episodes in patients with Parkinson’s disease (PD).

Methods

- An initial feasibility assessment determined that individual patient data (IPD) from the pivotal study of apomorphine sublingual film (apomorphine sublingual film and placebo arms) and summary statistics from the pivotal study of levodopa inhalation powder (SPAN-PD: levodopa inhalation powder 84-mg and placebo arms) were suitable for a matching-adjusted indirect comparison (MAIC) analysis.
- Patients from the apomorphine sublingual film pivotal study were selected for the MAIC using eligibility criteria from SPAN-PD, so that evaluable patients would have been qualified to enroll in the comparator study.
- To account for cross-study differences, the apomorphine sublingual film pivotal study population data were adjusted via propensity score weighting to match average baseline characteristics reported in SPAN-PD.
- Efficacy end points were change from predose in Unified Parkinson’s Disease Rating Scale (UPDRS) Part III score and reduction in total daily ‘OFF’ time at week 12.
- End points were anchored by the placebo arms of each study, and comparisons were conducted using Wald tests.

Results

- A total of 44 and 37 patients treated with apomorphine sublingual film and placebo (apomorphine sublingual film pivotal study), and 114 and 112 patients treated with levodopa inhalation powder and placebo (SPAN-PD), respectively, were included in the analysis.
- After matching, there were no statistical differences in change from predose in UPDRS Part III score at week 12 between treatments at earlier timepoints (i.e., 15–20 min and 30 min postdose), but the least squares (LS) mean difference was numerically favorable for apomorphine sublingual film versus levodopa inhalation powder at 30 min postdose (-8.38 vs. -3.92); at 60 min postdose, apomorphine sublingual film demonstrated a statistically significant improvement in UPDRS versus levodopa inhalation powder (-13.72 vs. -4.90; $p = 0.002$).
- After matching, the reduction in total daily ‘OFF’ time at week 12 was significantly larger for apomorphine sublingual film versus levodopa inhalation powder (LS mean difference, -1.32 vs. -0.01 h; $p = 0.013$).

Conclusion

- This MAIC enabled a statistically robust comparison of efficacy outcomes between apomorphine sublingual film and levodopa inhalation powder, and results demonstrated significant improvement in motor function scores at 60 min postdose and a significant reduction in daily ‘OFF’ time with apomorphine sublingual film versus levodopa inhalation powder.

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