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ADIS DRUG EVALUATION

Levodopa Inhalation Powder: A Review in Parkinson's Disease

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Abstract

Levodopa inhalation powder (Inbrija®) is approved for the intermittent treatment of OFF episodes in patients with Parkinson's disease (PD) treated with levodopa/dopa-decarboxylase inhibitor (LD-DCI) in the EU and specifically with carbidopa/levodopa in the USA. The approved dosage is 84 mg taken as needed up to five times a day. Administered via a breath-actuated inhaler, this formulation enables levodopa to bypass the gastrointestinal (GI) tract and, instead, rapidly enter the bloodstream through the pulmonary system. In the 12-week, double-blind, placebo-controlled, phase III SPAN-PD trial, as-needed levodopa inhalation powder 84 mg improved motor symptoms during OFF periods in PD patients (aged 30–86 years) treated with levodopa and carbidopa or benserazide. The likelihood of achieving an ON state 60 min postdose was significantly higher in the levodopa inhalation powder than the placebo group, with most patients in the levodopa inhalation powder group experiencing improvements in PD symptoms. Findings from longer-term, 52-week phase III studies were consistent with those from the SPAN-PD trial with regards to the treatment of OFF episodes. Levodopa inhalation powder was generally well tolerated and did not noticeably affect pulmonary function in PD patients. Providing a nonintrusive, convenient treatment method, levodopa inhalation powder is a promising option for the intermittent treatment of OFF episodes in patients with PD treated with a LD-DCI.

Levodopa inhalation powder: clinical considerations in PD

Dry powder formulation administered via breath-actuated inhaler
Bypasses the GI tract; rapidly enters the bloodstream through the pulmonary system
Improves motor symptoms during OFF episodes in PD patients receiving LD-DCI
Generally well tolerated; does not affect pulmonary function

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1 Introduction

Parkinson's disease (PD) symptoms worsen over time with the progressive loss of dopaminergic neurons in the substantia nigra [1]. Levodopa, a metabolic precursor to dopamine, has long been the mainstay of treatment for motor symptoms in PD and is particularly effective in the early stages of treatment [2]. However, long-term levodopa treatment is associated with the development of both motor and non-motor complications. Common motor complications include motor fluctuations, which involve the wearing-off of clinical response (i.e. transitions from "ON" to "OFF" states), and dyskinesia (uncontrolled, involuntary movement) [2]. Motor fluctuations worsen with advancing PD and long-term levodopa therapy; although motor fluctuations initially manifest in more predictable patterns (e.g. gradual shortening of ON durations with each dose) and may be addressed by means such as adjusting dosing intervals [3], parkinsonian symptoms may begin to return suddenly and unpredictably between doses over time [2, 4], necessitating rescue treatment.

Motor complications with oral levodopa are frequently associated with inconsistent or delayed drug delivery to the brain [4, 5]. Orally-administered levodopa competes with other neutral amino acids for uptake in the gastrointestinal (GI) tract wall as well as at the blood–brain

barrier, culminating in unpredictable or inconsistent clinical responses (including increasingly recurrent OFF periods) [5, 6]. GI dysfunction also manifests early in PD and, affecting 60–80% of patients, is one of the most common classes of non-motor PD symptoms [7, 8]; the use of orally-administered drugs in general may be limited in patients affected by dysphagia and other GI symptoms that impact drug absorption in the gut [8].

Levodopa delivery to the brain is further limited by the peripheral metabolism of levodopa into dopamine (via dopa-decarboxylation, the main metabolic pathway of levodopa [9]), which cannot cross the blood–brain barrier [10]. Although levodopa is therefore typically co-administered with a dopa-decarboxylase inhibitor (DCI; typically carbidopa or benserazide) to promote its absorption and reduce its peripheral metabolism (allowing for a reduced total levodopa dosage) [11], its terminal half-life ($t_{½}$) remains relatively short [1.1 vs 1.5–2.0 h for levodopa and levodopa-DCI (LD-DCI) [12]]. A reliable, fast-acting treatment to address motor fluctuations that emerge between doses is therefore an important facet in PD management, particularly in patients receiving long-term levodopa therapy.

Levodopa inhalation powder (Inbrija®) is formulated as a dry powder and administered orally via an inhaler, enabling rapid drug absorption via the pulmonary system [13, 14]. It is approved for the intermittent treatment of OFF episodes in patients with PD treated with a LD-DCI in the EU [15] or specifically with carbidopa/levodopa in the USA [13]. This review discusses therapeutic efficacy and tolerability data relevant to the use of levodopa inhalation powder in this setting, focusing on data relevant to the approved dose of 84 mg as needed up to five times a day; discussion of its use in other settings and at other dosages is beyond the scope of this review.

2 Pharmacological Properties of Levodopa Inhalation Powder

The pharmacodynamic properties of levodopa are well established and have been previously described elsewhere [5, 9]. Briefly, levodopa (after conversion to dopamine) binds to dopamine receptors in nigrostriatal neurons, relieving PD symptoms resulting from reduced dopaminergic innervation [5, 13]. The pharmacokinetic properties of levodopa inhalation powder are summarized in Table 1.

Levodopa inhalation powder is administered via the breath-actuated Inbrija® inhaler [13]. Each capsule contains levodopa 42 mg as a spray-dried powder, 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC; a pulmonary surfactant) and sodium chloride [13]. The dry powder particles (diameter 5–10 µm) are homogeneous, low in density and highly porous for optimal aerosolizability and lung deposition [16]. The inhaler delivered an emitted levodopa dose of 36.1 mg with a 42 mg levodopa powder capsule under in vitro testing conditions [13]. There was no significant change in the emitted dose when the flow rate and volume varied between 20 L/min/1 L and 90 L/min/2 L. In patients with PD ($n = 24$), the mean peak inspiratory flow rate was 64 L/min (range 39–98 L/min) during the ON state and 57 L/min (range 29–98 L/min) in the OFF state [13].

Table 1 Pharmacokinetic properties of levodopa inhalation powder [13, 15]

Dose-proportional pharmacokinetics up to 84 mg in healthy individuals in the presence of carbidopa
In the presence of carbidopa, $t_{½} = 2.3$ h after a single administration of levodopa inhalation powder 84 mg
Median $t_{max} \approx 30$ min after a single dose of levodopa inhalation powder 84 mg (vs 45 min with a single dose of carbidopa/levodopa 25 mg/100 mg immediate-release tablets)
Compared with oral carbidopa/levodopa 25/100 mg in fasted or fed states, plasma levodopa concentrations increased more rapidly with levodopa inhalation powder over doses of 10–50 mg [14]
Bioavailability of ≈ 70% relative to immediate-release oral levodopa tablets in healthy fasted individuals
Dose-normalized C_{max} of levodopa from levodopa inhalation powder is ≈ 50% of that following immediate-release oral levodopa tablets
Exposure following a single dose of levodopa inhalation powder 84 mg was similar between smokers and non-smokers (C_{max} and AUC) and between men and women (bodyweight-adjusted C_{max} and $AUC_{0–24}$)
In preclinical studies, there was no accumulation of levodopa after repeated dosing [22]
Apparent volume of distribution of 168 L for levodopa inhalation powder 84 mg
Major metabolic pathways are decarboxylation via dopa-decarboxylase (to form dopamine) and *O*-methylation via COMT (to form 3-*O*-methyldopa and 4-*O*-methyldopa); both processes occur in the CNS and in the peripheral circulation [9, 33]
Iron salts or multivitamins containing iron salts may reduce the bioavailability of levodopa by forming chelates with levodopa

$AUC_{(0–24)}$ area under the plasma concentration–time curve (from 0–24 h), *C_{max}* maximum plasma concentration, *COMT* catechol-*O*-methyltransferase, *PD* Parkinson's disease, *$t_{½}$* terminal elimination half-life, *t_{max}* time to maximum plasma concentration

3 Therapeutic Efficacy of Levodopa Inhalation Powder

The efficacy of levodopa inhalation powder 84 mg as an as-needed adjunct therapy (up to five times/day) for the treatment of OFF episodes in PD patients receiving LD-DCI treatment was assessed in a 12-week, randomized, double-blind, multinational, phase III study [SPAN-PD; intention-to-treat (ITT) population $n = 339$] [17]. The efficacy findings from SPAN-PD are supported by exploratory data from two longer-term (12-month), open-label phase III safety studies, CVT-301-004E [18] and CVT-301–005 [19] (Sect. 3.2). The CVT-301-004E study was an extension study to SPAN-PD and only included previous SPAN-PD participants in the ITT population; the safety population ($n = 312$; Sect. 4.1) also included treatment-naïve patients (including those in the observational cohort in CVT-301–005) and previous participants of a phase IIb dose-ranging study (CVT-301-003 [20]) and a phase I study (CVT-301-009 [21]), as long as they met the CVT-301-004E study eligibility criteria [18]. Some trial also included a levodopa inhalation powder 60 mg dose arm; however, as this dose is not approved, data pertaining to the dose are not discussed.

In SPAN-PD and the longer-term studies, eligible patients (aged 30–86 years) were on a stable LD-DCI regimen [levodopa with carbidopa or benserazide for ≥ 2 (immediate-release) or ≥ 6 (extended-release) weeks before screening where specified [17, 18]], receiving levodopa ≥ 3 times/day for a total intake of ≤ 1600 mg/day, with other PD medication stable and unchanged for ≥ 4 weeks before screening [17–19]. Patients had a modified Hoehn and Yahr (MHY) disease stage of 1–3 during an ON period, a Mini Mental State Examination (MMSE) score of ≥ 25, motor fluctuations in an ON state with an average daily OFF time of ≥ 2 h, and a ≥ 25% improvement in Unified Parkinson's Disease Rating Scale (UPDRS) Part III motor score from an OFF to ON state at screening [17–19]. In all three studies, patients were also required to have a forced expiratory volume at 1 s (FEV_1) of ≥ 50% and an FEV_1: forced vital capacity (FVC) ratio of ≥ 60% in an ON state [17–19].

Key exclusion criteria in the three studies were severe dyskinesia, history of drug or alcohol abuse and chronic respiratory disease within the last 5 years [17–19]. Other excluded patients include those with previous neurological treatment for PD [17] [including deep brain stimulation (DBS), unless performed > 6 months before study treatment [18]], a history of psychotic symptoms requiring treatment [17–19], and suicidal ideation or attempts < 12 months prior to the study [18, 19]. No other oral medications were to be used to manage OFF periods in SPAN-PD and CVT-301-004E [17, 18] and apomorphine was prohibited in all three studies [17–19].

3.1 Short-Term Pivotal Trial

Following a 5-week screening period, patients entered a 12-week treatment period (with clinic visits at baseline and at weeks 4, 8 and 12) in which they received levodopa inhalation powder 84 mg ($n = 114$), 60 mg ($n = 113$) or placebo ($n = 112$) as needed as an adjunct to a stable LD-DCI treatment regimen [17]. The study treatment was self-administered during the scheduled clinic visits and on an as-needed basis for OFF episodes off-site, up to five times during the day. Only a single dose (two capsules) of the study treatment was to be used for each OFF episode and, if an OFF state was not resolved within 45 min of receiving the dose, patients were to resume their usual PD medication. The primary efficacy endpoint in the SPAN-PD study was the effect on UPDRS Part III motor scores from predose to 30 min postdose at week 12 during an in-clinic OFF episode treated with levodopa inhalation powder 84 mg versus placebo. At week 12, key secondary endpoints were assessed hierarchically, as per the listed order in Table 2. Primary and secondary endpoints were analysed sequentially for the levodopa inhalation powder 84 mg dose, followed by the 60 mg dose [17].

At baseline, the SPAN-PD study participants had a mean of 3.5 OFF episodes per day, a mean daily OFF time of 5.5 h and an average daily levodopa intake of 828 mg [17]. The majority of patients in the levodopa inhalation powder 84 mg and placebo groups (94% and 95%) had a FEV_1 of ≥ 60% and an FEV_1:FVC ratio of ≥ 70%. In all treatment groups, patients received a mean number of ≈ 2 doses/day throughout the study [17].

Adjunctive as-needed levodopa inhalation powder 84 mg improved motor symptoms during OFF periods in PD patients receiving LD-DCI treatment, as indicated by the significant mean reduction in UPDRS motor score from predose to 30 min postdose evident with the drug relative to placebo at 12 weeks (primary endpoint; Table 2) [17]. While a numerical difference consistent with those at 30 min and 10 min postdose was observed, the least-squares mean (LSM) change in UPDRS motor score was not statistically significant at 20 min postdose with levodopa inhalation powder 84 mg versus placebo. Although the subsequent endpoints in the hierarchical sequence were therefore ineligible for declaring statistical significance, an improvement was seen with respect to the LSM change in UPDRS motor score at 10 min postdose with levodopa inhalation powder 84 mg compared with placebo (nominal $p < 0.05$) (Table 2). The improvement in UPDRS motor score was maintained with levodopa inhalation powder 84 mg at 60 min postdose (LSM change from baseline − 10.59 vs − 5.65 with placebo; nominal $p = 0.002$) [22]. The patient-reported LSM changes in total daily OFF time from baseline were similar between

Table 2 Efficacy of levodopa inhalation powder 84 mg at 12 weeks in patients with Parkinson's disease in the phase III SPAN-PD trial

Endpoint	LIP ($n=114$)	Placebo ($n=112$)	LIP vs placebo (95% CI)
Change in UPDRS motor score at 30 min postdose (LSM)	−9.83	−5.91	−3.92[a,b] (−6.84 to −1.00)*
ON state at 60 min postdose (% of pts)	58	36	OR 2.65 (1.48–4.76)*
Change in UPDRS motor score at 20 min postdose (LSM)	−9.04	−6.49	−2.55[a,c] (−5.22 to 0.13)
Improved PGI-C score (% of pts)	71	46	OR 2.94 (1.62–5.33)[††]
Change in UPDRS motor score at 10 min postdose (LSM)	−6.45	−4.18	−2.26[a] (−4.48 to −0.04)[†]
Change in total daily OFF state time from baseline (LSM) (h)	−0.47	−0.48	−0.01[a] (−0.55 to 0.56)

Intent-to-treat analysis for this double-blind, multinational trial [17, 34]. Primary and key secondary endpoints are shown in hierarchical order

LIP levodopa inhalation powder 84 mg, *LSM* least squares mean, *OR* odds ratio, *PGI-C* Patient Global Impression of Change rating scale, *pts* patients, *UPDRS* Unified Parkinson's Disease Rating Scale

*$p<0.01$ vs placebo

[†]$p<0.05$, [††]$p<0.001$ vs placebo (nominal)

[a]LSM difference between LIP vs placebo

[b]Primary endpoint

[c]As this endpoint was not statistically significant, all subsequent hierarchical endpoints were ineligible for being declared statistically significant

the levodopa inhalation powder 84 mg and placebo groups (Table 2) [17].

The odds of being able to maintain an ON state 60 min postdose with levodopa inhalation powder 84 mg was > 2.5 times that of placebo, with ≈ 1.6 times as many levodopa inhalation powder 84 mg than placebo recipients achieving this outcome (Table 2) [17]. Relative to placebo recipients, patients treated with levodopa inhalation powder 84 mg had almost 3 times the odds of reporting improvements in PD symptoms with respect to Patient Global Impression of Change (PGI-C) score, with ≈ 1.5 times as many patients in the levodopa inhalation powder 84 mg group reporting improvements in PGI-C score (Table 2) [17].

3.2 Longer-Term Trials

Patients were randomized to receive levodopa inhalation powder 84 or 60 mg in CVT-301-004E (ITT population $n=297$) [18], and to receive levodopa inhalation powder 84 mg or be placed into an observational cohort (and receive standard oral treatment for PD) in CVT-301-005 (ITT population $n=398$) [19]. Select exploratory efficacy endpoints in these studies (assessed at weeks 4, 12, 24, 36 and 52) included the proportions of patients achieving an ON state 60 min postdose and with an improved PGI-C score, and changes from baseline in total daily OFF time, ON time without dyskinesia, and (in CVT-301-005 only) UPDRS Part III motor score [18, 19]. The average number of levodopa inhalation powder 84 mg doses taken during the study was 1.94/day and 2.3/day in CVT-301-004E [18] and CVT-301-005 [19].

Longer-term efficacy findings from the CVT-301-004E [18] and CVT-301-005 [19] studies indicated that the treatment of OFF times with levodopa inhalation powder 84 mg continued to be effective after 52 weeks [18, 19]. Over weeks 4–52, most patients in the levodopa inhalation powder 84 mg group (71–79% and 80–85% in CVT-301-004E and CVT-301-005) had maintained an ON state at 60 min postdose [18, 19]. Changes from baseline in ON times without dyskinesia with levodopa inhalation powder 84 mg were +0.18 and +0.40 h at weeks 4 and 52 in CVT-301-004E (data from other weeks not reported) [18] and ranged from +1.01 to +1.49 h at weeks 4–52 in CVT-301-005 [19]. The LSM changes in total daily OFF time over weeks 4–52 with levodopa inhalation powder 84 mg ranged from −0.38 to −0.92 h in CVT-301-004E [18] and −1.32 to −1.42 h in CVT-301–005 [19]. In CVT-301–005, mean changes in UPDRS motor score from predose to 10, 20, 30 and 60 min postdose remained consistent when measured in weeks 4–52 (data not reported) [19].

Improvements in PGI-C score were also reported in most patients receiving levodopa inhalation powder 84 mg at weeks 4–52 in CVT-301-004E (67–92%) [18] and at weeks 12, 24 and 52 in CVT-301-005 (77–88%; data from other weeks not reported) [19]. Post hoc data from CVT-301-004E excluding early withdrawers indicated that 84% of patients receiving levodopa inhalation powder 84 mg ($n=113$ without early withdrawers) reported improvements in PGI-C score [18].

4 Tolerability of Levodopa Inhalation Powder

Levodopa inhalation powder 84 mg was generally well tolerated in patients with PD in the 12-week SPAN-PD study [17] and the 52-week CVT-301-004E [23] and CVT-301-005 [19] studies. Patients received an average of ≈ 2 doses/day [17, 19, 23] and, in SPAN-PD, 50% and 26% of levodopa inhalation powder 84 mg recipients received 4 and 5 doses/day at least once during the study [17]. After 12 weeks, adverse events (AEs) occurred in 58% and 44% of patients in the levodopa inhalation powder 84 mg and placebo groups in SPAN-PD [17]. In the longer-term studies, AEs were reported in 72% [23] and 71% [19] of levodopa inhalation powder 84 mg recipients, and in 58% of patients in the observational cohort in CVT-301-005 [19]. Most AEs occurring in the levodopa inhalation powder 84 mg groups were mild or moderate in severity [17, 19, 23].

Cough was the most common AE among patients who received levodopa inhalation powder 84 mg in SPAN-PD (15 vs 2% of placebo recipients) and was considered to be drug-related [i.e. a treatment-related AE (TRAE)] [17]. Cough was also among the most common TRAEs in CVT-301-005 (with others including dyskinesia, throat irritation and discoloured sputum [19]) and was the most commonly reported treatment-emergent AE (TEAE) in CVT-301-004E (15%) [23] and CVT-301-005 (13%) [19]. Across the studies, most cases of cough with levodopa inhalation powder 84 mg were mild [17, 19, 23] or moderate [17, 23] in severity and, where specified, occurred in the first 30 days of treatment [17, 19]. Other common AEs (≥ 5% incidence) among levodopa inhalation powder 84 mg recipients included upper respiratory tract infection (URTI) [6 vs 3% of placebo recipients], nausea (5 vs 3%) and discoloured sputum (5 vs 0%) in SPAN-PD [17] and fall (11% [23]; 8% [19]), URTI (8% [23]; 5% [19]), nasopharyngitis (7% [19]) and dyskinesia (6% [19, 23]) in CVT-301-004E [23] and/or CVT-301–005 [19].

Approximately 5% and 3% of levodopa inhalation powder 84 mg and placebo recipients discontinued treatment due to an AE in SPAN-PD [17]. Of the patients who received longer-term levodopa inhalation powder 84 mg, 9% withdrew from CVT-301-004E [23] and from CVT-301-005 [19] because of AEs. Cough was the most common reason for AE-related treatment discontinuation in patients treated with levodopa inhalation powder 84 mg (2 vs 0% of placebo recipients in SPAN-PD [17]; 2% in CVT-301-004E [23] and 1% in CVT-301-005 [19]).

Serious AEs (SAEs) in SPAN-PD occurred in two (2%) levodopa inhalation powder 84 mg and three (3%) placebo recipients [17]. One SAE (atrial fibrillation) in the levodopa inhalation powder 84 mg group was considered to be possibly treatment-related [17]. Of the 13 (8%) levodopa inhalation powder 84 mg patients who experienced a SAE in CVT-301-004E, one experienced an SAE possibly related to treatment (impulse control disorder) which was later resolved [23]. Among the SAEs in the levodopa inhalation powder 84 mg group in CVT-301-005 (16 vs 10% in the observational cohort), pulmonary embolism and dopamine dysregulation syndrome (1 patient each) were possibly related to levodopa inhalation powder 84 mg [19].

In the levodopa inhalation powder 84 mg group in SPAN-PD, numerically more patients aged ≥ 65 years ($n = 56$) than those aged < 65 years ($n = 58$) experienced cough (25 vs 5%), URTI (11 vs 2%), nausea (7 vs 3%), vomiting (4 vs 2%), pain in the extremities and discoloured nasal discharge (4 vs 0% for both AEs) [13].

A two-way crossover phase I study ($n = 36$) was conducted to assess the safety of treating morning OFF episodes with levodopa inhalation powder 84 mg in patients receiving carbidopa/levodopa (i.e. while plasma carbidopa levels are low) [21]. Similar to the phase III study findings, AEs that occurred in this study were mostly mild in severity and resolved without treatment. There did not appear to be a correlation between carbidopa concentrations and AEs (including dyskinesia) [21].

4.1 Pulmonary Function

Levodopa inhalation powder 84 mg did not appear to affect pulmonary function in patients with PD. At 12 weeks, spirometry data with respect to FEV_1, FVC, FEV_1: FVC and diffusion capacity of the lungs for carbon monoxide (DLco) were not noticeably different between the levodopa inhalation powder 84 mg and placebo groups of SPAN-PD (data not reported) [17]. After 52 weeks in CVT-301-005, the mean change in FEV_1 from baseline was − 0.11 L and − 0.12 L in the levodopa inhalation powder 84 mg and observational cohorts, and the mean change in DLco was − 0.38 mL/min/mmHg and − 0.72 mL/min/mmHg [19]. Although the LSM changes in FEV_1: FVC from baseline at 6 and 12 months were significantly lower in the levodopa inhalation powder 84 mg than observational cohort (LSM between-group difference 1.3 and 0.8; $p \leq 0.048$), no significant differences were observed at months 3 and 9 [19]. Similar findings were reported for the levodopa inhalation powder 84 mg group in CVT-301-004E (mean changes from baseline in FEV_1 − 0.097 L, FVC − 0.089 L, DLco − 0.665 mL/min/mmHg) [23].

Because of the risk of bronchospasm, levodopa inhalation powder is not recommended in patients with asthma, chronic obstructive pulmonary disease, or other chronic lung diseases [13, 15].

5 Dosage and Administration of Levodopa Inhalation Powder

Levodopa inhalation powder is approved for the intermittent treatment of OFF episodes in patients with PD treated with a LD-DCI in the EU [15] or with carbidopa/levodopa in the USA [13]. Levodopa inhalation powder capsules are for oral inhalation only, must only be administered via the Inbrija® inhaler, and should only be taken when symptoms of an OFF episode start to return. The recommended dosage is oral inhalation of the contents of two 42 mg capsules (84 mg) as needed, up to five times/day. The maximum dose per OFF period is 84 mg and the maximum daily dosage is 420 mg [13, 15]. According to EU prescribing information, no dose adjustment is required based on smoking status [15].

Levodopa inhalation powder is contraindicated in patients currently taking a nonselective monoamine oxidase (MAO) inhibitor (e.g. phenelzine, tranylcypromine) or who have recently (within 2 weeks) taken a nonselective MAO inhibitor; hypertension can occur if these drugs are used concurrently [13, 15]. Local prescribing information should be consulted for detailed information, including other contraindications, precautions, drug interactions, use in special patient populations, and other risk factors and considerations relevant to levodopa inhalation powder treatment.

6 Current Status of Levodopa Inhalation Powder in Parkinson's Disease

Motor fluctuations in PD patients receiving longer-term oral levodopa therapy are associated with inconsistent levodopa delivery to the brain (Sect. 1). Strategies to minimize the risk of motor fluctuations in these patients include (but are not limited to) adjusting levodopa dose intervals based on durations of clinical response, administering levodopa in a fasted state, using extended-release formulations of levodopa-based drugs and co-administering levodopa with drugs that extend its presence and duration of action [e.g. DCIs and catechol-*O*-methyltransferase (COMT) and MAO-B inhibitors] and adjusting their dose or discontinuing them as required [24]. Levodopa/carbidopa enteral suspension (ES) or continuous subcutaneous apomorphine infusions are recommended to treat inadequately-controlled motor complications in advanced PD [3, 25]. DBS can be used in patients aged < 70 years whose motor symptoms remain unresolved despite optimal therapy and are otherwise healthy [3, 25, 26]; DBS has a greater risk profile for AEs in elderly patients (age > 70 years), but may be considered as second-line treatment in this population [25]. However, motor complications become inevitable with advanced PD; while clinical responses with levodopa are more sustained in early PD as dopamine is stored in dopaminergic neurons, they become shorter in duration with progressing PD and neuronal loss [27]. As such, fast-acting and efficient rescue treatments for OFF episodes are a necessary part of PD management.

The formulation of levodopa inhalation powder facilitates a rapid clinical response as it bypasses the GI tract and allows levodopa to rapidly enter the bloodstream through the pulmonary system (Sect. 2) [14]; in contrast, the absorption of oral levodopa in the gut is impacted by various digestion-related factors as well as PD-related GI dysfunction, leading to unpredictable clinical responses (Sect. 1). With PD patients in an OFF state being seen to be able to operate dry powder inhalers [28], levodopa inhalation powder is self-administered as required at the onset of an OFF episode. Apomorphine is another approved medication to treat OFF episodes but is administered through the less convenient route of subcutaneous injection [29, 30]. In addition, apomorphine is associated with a range of potential adverse effects and requires premedication with an antiemetic [29]. A soluble formulation of levodopa/benserazide is also available in the EU for the treatment of OFF episodes due to its rapid onset of action; however, it requires the discontinuation of other levodopa-based or LD-DCI therapy [31].

Findings from phase III clinical trials indicated that levodopa inhalation powder 84 mg was effective as an as-needed adjunctive therapy to treat OFF episodes in PD patients aged 30–86 years receiving LD-DCI treatment (Sect. 3). In SPAN-PD, improvements in motor function were seen at 30 min postdose with levodopa inhalation powder 84 mg; motor function appeared to be improved at 10 min postdose, although this finding was of nominal statistical significance (Sect. 3.1). A significantly greater proportion of patients receiving levodopa inhalation powder 84 mg had also achieved an ON state at 60 min postdose. While of nominal statistical significance, improvements in PD symptoms were reported in a greater proportion of patients receiving levodopa inhalation powder 84 mg than those receiving placebo (Sect. 3.1). Although efficacy analyses in longer-term studies were exploratory, findings relevant to treatment with levodopa inhalation powder 84 mg were consistent with those seen in SPAN-PD (Sect. 3.2).

Levodopa inhalation powder 84 mg was generally well tolerated in clinical trials of up to 52 weeks' duration, with most AEs being of mild or moderate severity (Sect. 4). Cough, which was the most common TRAE, mostly occurred in the first 30 days of treatment (Sect. 4) and pulmonary function was not affected; spirometry findings were similar at 12 and 52 weeks (Sect. 4.1). While preclinical pharmacokinetic studies showed no accumulation of levodopa after repeated dosing of levodopa inhalation powder (Table 1), dyskinesia, which is associated with long-term levodopa treatment [32], was among the most common TRAEs with the inhalation powder

in these studies (Sect. 4). Similar tolerability was evident with levodopa inhalation powder 84 mg when used to treat morning OFF periods in a phase I study, with no correlation found between AEs and carbidopa concentrations (Sect. 4); larger, more robust studies would be needed to confirm this.

Further long-term clinical experience would be beneficial in more definitively establishing the efficacy and tolerability profile of levodopa inhalation powder in treating OFF episodes, particularly as OFF episodes become more recurrent with progressing PD and continued levodopa treatment. While OFF episodes were generally managed with two doses/day in the discussed studies, further data may determine whether a higher dosing frequency (such as the maximum recommended five times/day) may be needed over time. Robust studies investigating the use of levodopa inhalation powder in patients with severe dyskinesia (a population excluded from the phase III studies discussed in Sect. 3) may be valuable. Moreover, given that levodopa inhalation powder is indicated in patients receiving levodopa-based therapy (and given the occurrences of treatment-related dyskinesia in the discussed studies), studies to help determine whether levodopa inhalation powder further increases the risk for such levodopa-related complications would be of interest. Direct head-to-head trials are required to determine the relative efficacy and tolerability of levodopa inhalation powder as a rescue therapy option compared with apomorphine and with levodopa/benserazide.

In conclusion, levodopa inhalation powder is effective in the treatment of OFF periods and is generally well tolerated. While further clinical experience is required to determine its long-term efficacy and safety, levodopa inhalation powder is a promising option for the intermittent treatment of OFF episodes in patients with PD treated with a LD-DCI.

Data Selection Inhaled levodopa: 233 records identified	
Duplicates removed	77
Excluded during initial screening (e.g. press releases; news reports; not relevant drug/indication; preclinical study; reviews; case reports; not randomized trial)	66
Excluded during writing (e.g. reviews; duplicate data; small patient number; nonrandomized/phase I/II trials)	56
Cited efficacy/tolerability articles	8
Cited articles not efficacy/tolerability	26
Search Strategy: EMBASE, MEDLINE and PubMed from 1946 to present. Clinical trial registries/databases and websites were also searched for relevant data. Key words were inhaled levodopa, Inbrija, CVT301, Parkinson's disease. Records were limited to those in English language. Searches last updated 4 April 2020	

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Compliance with Ethical Standards

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