CADTH

CADTH COMMON DRUG REVIEW

Clinical Review Report

LEVODOPA/CARBIDOPA (DUODOPA)

(ABBVIE CORPORATION)

Indication: For the treatment of patients with advanced levodopa-responsive Parkinson's disease:

- who do not have satisfactory control of severe, debilitating motor fluctuations and hyper-/dyskinesia despite optimized treatment with available combinations of Parkinson's medicinal products, and
- for whom the benefits of this treatment may outweigh the risks associated with the insertion and long-term use of the percutaneous endoscopic gastrostomy-jejunostomy (PEG-J) tube required for administration

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Abbreviations

ADL	activities of daily living
AE	adverse event
ANCOVA	analysis of covariance
AUROC	area under the receiver operating characteristics
CDR	CADTH Common Drug Review
CEDAC	Canadian Expert Drug Advisory Committee
CGI-I	Clinical Global Impression – Improvement
CGI-S	Clinical Global Impression – Severity
CI	confidence interval
CISI-PD	Clinical Impression of Severity Index for Parkinson Disease
COMT	catechol-O-methyltransferase
DB	double-blind
DBS	deep brain stimulation
DPAC-FWG	Drug Policy Advisory Committee Formulary Working Group
EPD	early Parkinson disease
EQ-5D-3L	EuroQol 5-Dimensions 3-Levels questionnaire
EQ VAS	EuroQol visual analogue scale
FAS	full analysis set
GI	gastrointestinal
HRQoL	health-related quality of life
HY	Hoehn and Yahr
ICC	interclass coefficient
IR	immediate-release
LCIG	levodopa/carbidopa intestinal gel
LOCF	last observation carried forward
LS	least squares
LSMD	least squares mean difference
MAO-B	monoamine oxidase type B
MCID	minimal clinically important difference
MDS	Movement Disorder Society
MMRM	mixed-effects models for repeated measures
NJ	nasojejunal
OLC	oral levodopa/carbidopa
PAA	Parkinson Association of Alberta
PBO	placebo
PC	Parkinson Canada
PD	Parkinson disease
PDHD	Parkinson disease home diary
PDQ-39	39-Item Parkinson's Disease Questionnaire
PDQSI	Parkinson's Disease Questionnaire — summary index
PEG-J	percutaneous endoscopic gastrostomy with jejunal extension

PGI-S	Patient Global Impression – Severity
PSBC	Parkinson Society British Columbia
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomized controlled trial
SAE	serious adverse event
SD	standard deviation
SE	standard error
SES	Schwab and England Scale
SF-36	Short Form (36) Health Survey
TEAE	treatment-emergent adverse event
UPDRS	Unified Parkinson's Disease Rating Scale
VAS	visual analogue scale
ZBI	Zarit Burden Interview

Drug	Levodopa/carbidopa (Duodopa)
Indication	For treatment of patients with advanced levodopa-responsive Parkinson's disease: • who do not have satisfactory control of motor fluctuations and hyper-/dyskinesia despite optimized treatment with oral therapy, and • for whom the benefits of this treatment may outweigh the risks associated with the insertion and long-term use of the percutaneous endoscopic gastrostomy-jejunostomy (PEG-J) tube required for administration
Reimbursement Request	As per indication
Dosage Form	100 mL of gel contains 2,000 mg levodopa and 500 mg carbidopa (monohydrate)
NOC Date	1/3/2007
Manufacturer	AbbVie Corporation

Executive Summary

Introduction

Parkinson disease (PD) is the second most common neurodegenerative disorder after Alzheimer disease.[1] The characteristic features of PD include resting tremor, rigidity, bradykinesia, and postural instability leading to loss of control of voluntary movement.[2-4] The underlying cause of motor symptoms is a combination of chronic degeneration of the dopaminergic neurons in the nigrostriatal region of the brain and depletion of dopamine.[4] Further, progressive loss of dopaminergic neurons results in an inability to store and regulate dopamine function in the brain.[4] Therefore, as PD progresses, impairment in motor functions may worsen over time and can result in debilitating disability. PD is also associated with non-motor symptoms, such as neuropsychiatric symptoms, gastrointestinal (GI) symptoms, sleep disturbances, urinary dysfunction, pain, and impulse control disorders.[5,6]

A number of dopaminergic anti-PD medications are marketed worldwide and in Canada. Levodopa, a precursor of dopamine, is the first-line treatment due to its effectiveness in minimizing the motor-related symptoms of PD — including tremor, rigidity, and bradykinesia — by restoring dopamine deficiency at the nigrostriatal region in the brain.[7] The Canadian Guidelines on Parkinson's Disease recommend that oral levodopa be given in combination with any of the following based on PD stage and tolerability: in fixed combination with dopa decarboxylase inhibitors (carbidopa or benserazide), monoamine oxidase type B (MAO-B) inhibitors (selegiline and rasagiline), or anticholinergics (trihexyphenidyl and procyclidine); or in fixed combination with carbidopa and entacapone, a catechol-O-methyltransferase (COMT) inhibitor.[7] These adjunct drugs prevent rapid metabolism of levodopa into dopamine, whose short plasma half-life (1.5 hours) improves the bioavailability of levodopa and reduces the peripheral side effects associated with levodopa treatment, such as nausea and vomiting. The most common early side effects associated with levodopa include nausea, somnolence, dizziness, and headache. Long-term administration may lead to confusion, hallucinations, delusions, agitation, psychosis, and orthostatic hypotension, particularly in older patients.[8]

Duodopa is a levodopa/carbidopa intestinal gel (LCIG) formulation that is infused directly into the proximal small intestine through a percutaneous endoscopic gastrostomy-jejunostomy (PEG-J) tube intended to mitigate the influences on the absorption rate of intermittent oral levodopa/carbidopa (OLC) dosing and unpredictable gastric emptying associated with PD by providing relatively constant plasma concentrations of levodopa.[9] According to the Health Canada–approved indication, LCIG can be used for the treatment of patients with advanced levodopa-responsive PD who do not have satisfactory control of severe, debilitating motor fluctuations and hyper-/dyskinesia despite optimized treatment with available combinations of PD medicinal products, and for whom the benefits of this treatment may outweigh the risks associated with the insertion and long-term use of the PEG-J tube required for administration.[9]

A previous review of the use of LCIG for PD in 2009 by CADTH Common Drug Review (CDR) led to the recommendation by the CADTH Canadian Expert Drug Advisory Committee (CEDAC) that LCIG "not be listed" due to:

- The manufacturer's reported incremental cost per quality-adjusted life-year (QALY) estimate for Duodopa of [redacted] to [redacted] compared with conventional oral drug therapies. The manufacturer requested that specific results from the economic evaluation remain confidential pursuant to CDR confidentiality guidelines. Other published cost per QALY estimates for Duodopa were reported at approximately $1 million dollars.
- The quality of two trials considered by the Committee was limited by open-label designs, high proportions of withdrawals in trials of small sample size, and patient populations that were not representative of those most likely to use Duodopa. Therefore, given concerns with the quality of these trials, the relevance of the results was limited.

The current CDR review was undertaken in response to a request from the drug plans that participate in the CDR review process that the use of LCIG in PD be re-reviewed in light of the availability of new evidence. Therefore, for the current review, new clinical evidence that has become available since the CDR review in 2009 was considered for inclusion in a systematic review to assess the efficacy and harms of LCIG for the treatment of patients with advanced levodopa-responsive PD who do not have satisfactory control of severe, debilitating motor fluctuations and hyper-/dyskinesia despite optimized treatment with available combinations of PD medicinal products, and for whom the benefits of this treatment may outweigh the risks associated with the insertion and long-term use of the PEG-J tube required for administration.

Results and Interpretation

Included Studies

New clinical evidence available since the previous CDR review of Duodopa for PD comprised 20 trials.

Double-Blind, Randomized Controlled Trial

Study 001/002 (N = 71) was a DB, double-dummy, active-controlled, multi-centre, multinational, phase III superiority randomized controlled trial (RCT) that recruited patients from North America (excluding Canada). The study objective was to evaluate the efficacy and safety of LCIG for the treatment of patients with advanced levodopa-responsive PD who do not have satisfactory control of severe, debilitating motor fluctuations and hyper-

/dyskinesia despite optimized treatment with available combinations of Parkinson medicinal products, and for whom the benefits of this treatment may outweigh the risks associated with the insertion and long-term use of the PEG-J tube required for administration. Patients were randomized to a 1:1 ratio of optimally titrated LCIG (20 mg/mL levodopa and 5 mg/mL carbidopa monohydrate solution) in addition to placebo immediate-release (IR) OLC capsules or optimally titrated IR OLC 100 mg/25 mg capsules in addition to placebo LCIG. The primary efficacy outcome was change from baseline to final visit (week 12) in the mean number of “off” hours recorded in the Parkinson disease home diary (PDHD) during the three consecutive days prior to study visit, normalized to a 16-hour waking day. The predefined key secondary outcome was change from baseline to final visit (week 12) in the mean number of normalized (16-hour waking day) “on” hours without troublesome dyskinesia (defined as a composite of "on" time without dyskinesia and "on" time with non-troublesome dyskinesia). Other secondary outcomes included change from baseline in the 39-item Parkinson’s Disease Questionnaire (PDQ-39) summary index score, the Clinician Global Impression – Improvement (CGI-I) score, the Unified Parkinson's Disease Rating Scale (UPDRS) Part II (activities of daily living [ADL] subscore) and Part III (motor subscore), the Zarit Burden Interview (ZBI) score, and the EuroQol 5-Dimensions 3-Levels (EQ-5D-3L) summary index score.

Although some methodological limitations were highlighted, no major limitations were identified in Study 001/002. Some of the noted limitations included differences in PD severity between treatment groups at baseline, the potential for unblinding due to non-compliance with active IR OLC capsules in the comparator group, and the lack of information about the adequacy of caregiver report as a proxy for patient-reported “off” time.

Open-Label, Non-Comparative Study (Study 004)

Study 004 (N = 354) was a non-comparative, multinational, multi-centre, open-label, long-term safety study that recruited patients from North America (including Canada) and western Europe. Patients included in this study were not previously treated with LCIG in Study 001/002. The study objective was to evaluate the safety of LCIG for the treatment of patients with advanced levodopa-responsive PD over a 54-week period. LCIG was delivered as an aqueous solution containing 20 mg/mL levodopa and 5 mg/mL carbidopa monohydrate packaged in 100 mL cassettes administered as a morning bolus dose followed by continuous infusion at a constant rate for the remainder of each patient’s waking day (approximately 16 hours) with additional rescue doses during the day, if clinically indicated. The primary objective was to evaluate the long-term safety of LCIG based on adverse events (AEs), device complications, and number of completers. All AEs were considered as treatment-emergent adverse events (TEAEs), defined as those that began or worsened from the time of nasojejunal (NJ) tube insertion until 30 days after PEG-J removal. Long-term efficacy (as measured by “off” time, “on” time with and without troublesome dyskinesia, and UPDRS) and quality of life (QoL) (as measured by PDQ-39, EQ-5D-3L, EuroQol visual analogue scale [EQ VAS], and CGI-I) were evaluated as secondary end points. Key limitations of Study 004 include its open-label and non-comparative study design.

Additional Open-Label, Non-Comparative Studies

Patients who completed Study 001/002 had the option to enrol in an optional 12-month open-label safety extension study (Study 003, N = 62). Furthermore, patients who completed either Study 003 or Study 004 were able to enrol in Study 005 (N = 262) for up to five years of follow-up. Study 003 and Study 005 are both summarized in Appendix 6. A

total of 16 other prospective, open-label, non-comparative trials were also identified in the CDR systematic review. [10-25] The sample sizes of these trials ranged between nine and 375 enrolled patients; follow-ups ranged between four and 36 months. Treatment with LCIG was administered to all patients. Change from baseline to the last study visits was evaluated for relevant outcomes. Key limitations of the trials (including Study 003 and Study 005) include their open-label and non-comparative study design.

Efficacy

Double-Blind, Randomized Controlled Trial

Compared with IR OLC, LCIG was associated with a statistically significant reduction in daily normalized "off" time at week 12 (the primary outcome) completed through the PDHD. The adjusted least squares mean difference (LSMD) in change from baseline was –1.91 hours (95% CI, –3.05 to –0.76; *P* = 0.0015) in favour of LCIG. Furthermore, results of the sensitivity analyses (using mixed-effects models for repeated measures to impute data and sensitivity analyses with varying covariates requested by the FDA) were mostly consistent with the primary analysis for this outcome. Given that the benefit associated with treatment with LCIG exceeds the reported minimal clinically important difference (MCID) (–1.00 hours), the improvement in "off" time reported in Study 001/002 would be considered clinically meaningful.

The evaluation of "off" time as the primary end point in Study 001/002 was supported by the evaluation of a key secondary end point (adjusted for multiple statistical testing), normalized "on" time without troublesome dyskinesia (a composite of "on" time without dyskinesia and "on" time with non-troublesome dyskinesia). Overall, LCIG was also associated with a statistically significant improvement in daily normalized "on" time without troublesome dyskinesia at week 12. The adjusted LSMD in change from baseline was 1.86 hours (95% CI, 0.56 to 3.17; *P* = 0.0059) in favour of the LCIG. When looking at the two components of the composite separately, it appeared that the results were driven primarily by the increase in "on" time without dyskinesia (adjusted LSMD in change from baseline: 2.28 hours [95% CI, 0.47 to 4.09; *P* = 0.0142]), since the change in "on" time with non-troublesome dyskinesia was not statistically significant (–0.73 [95% CI, –2.22 to 0.76; *P* = 0.3294]). Overall, the result of the key secondary outcome was also consistent with the primary analysis; however, no MCID was identified for the change in "on" time.
No adjustments for multiple statistical testing were made for the individual components of this end point.

Other secondary outcome measures (adjusted for multiple statistical testing) included change from baseline in PDQ-39 summary index score, CGI-I score, UPDRS Part II (ADL subscore), UPDRS Part III (motor subscore), EQ-5D-3L summary index score, and the ZBI score. Compared with IR OLC, LCIG was associated with a statistically significant and clinically meaningful reduction in favour of the study drug for both the PDQ-39 summary index score (adjusted LSMD in change from baseline was –7.0 [95% CI, –12.6 to –1.4; *P* = 0.0155] compared with an MCID of –1.6) and the UPDRS Part II score (adjusted LSMD in change from baseline was –3.0 [95% CI, –5.3 to –0.8; *P* = 0.0086] compared with an MCID of –2.3). The results for the CGI-I score were also statistically significant in favour of the LCIG (adjusted LSMD in change from baseline was –0.7 [95% CI, –1.4 to –0.1; *P* = 0.0258]); however, no MCID was identified. Therefore, the clinical meaningfulness of the change in CGI-I remains unclear. No statistically significant differences between treatments were reported for the UPDRS Part III (adjusted LSMD in change from baseline was 1.4 [95% CI, –2.8 to 5.6; *P* = 0.5020]).

Study 001/002 also evaluated health-related quality of life (HRQoL) using the EQ-5D-3L summary index score; the adjusted LSMD in change from baseline was 0.07 [95% CI, –0.01 to 0.15; *P* = 0.0670]). For caregiver burden using the ZBI score, the adjusted LSMD in change from baseline was –4.5 [95% CI, –10.7 to 1.7; *P* = 0.1501]). These end points should be considered exploratory despite being part of the testing hierarchy given that they were evaluated subsequent to failure of a prior end point in the hierarchy (UPDRS Part III); therefore the clinical importance of these changes also remains unclear.

Changes in the mean daily normalized "off" time and "on" time without troublesome dyskinesia at week 54 compared with baseline in Study 004 were –4.4 hours (2.9, *P* < 0.001) and 4.8 hours (3.4, *P* < 0.001), respectively. The mean change in "on" time with troublesome dyskinesia was –0.4 (2.8, *P* = 0.023). Changes in the mean UPDRS Part II score, PDQ-39 summary index score, EQ-5D summary index score, and EQ VAS were -4.4 (6.5, *P* < 0.001), –6.9 (14.1, *P* < 0.001), 0.064 (0.203, *P* < 0.001), and 14.0 (24.8, *P* < 0.001), respectively. Efficacy outcomes in Study 004 were not adjusted for multiple statistical comparisons.

Harms

Overall, 95% and 100% of patients experienced AEs in the LCIG + placebo (PBO) IR OLC capsules group and the PBO LCIG + IR OLC capsules group, respectively. The frequencies of AEs were relatively similar across treatment groups. The most common AEs were falls (11% versus 12%), atelectasis (8% versus 0%), anxiety (8% versus 3%), confusional state (8% versus 3%), oedema peripheral (8% versus 0%), oropharyngeal pain (8% versus 0%), and upper respiratory tract infection (8% versus 0%) in the LCIG + PBO IR OLC capsules and PBO LCIG + IR OLC capsules groups, respectively. Fewer patients experienced serious adverse events (SAEs) in the LCIG + PBO IR OLC capsules group compared with the PBO LCIG + IR OLC capsules group (14% versus 21%, respectively). The most common SAEs were confusional state (5% versus 0%) and pneumonia (0% versus 6%) in the LCIG + PBO IR OLC capsules and PBO LCIG + IR OLC capsules groups, respectively.

Overall, one patient (3%) and two patients (6%), respectively, withdrew due to AEs in the LCIG + PBO IR OLC capsules and PBO LCIG + IR OLC capsules groups. The most common reasons were hallucination and psychotic disorder (3% versus 0%, each) and peritonitis, post-procedural complication, and post-procedural discharge (0% versus 3%, each) in the LCIG + PBO IR OLC capsules and PBO LCIG + IR OLC capsules groups, respectively. No deaths were reported in Study 001/002.

Most patients experienced device-related complications across both treatment groups (92% and 85% in the LCIG + PBO IR OLC capsules and PBO LCIG + IR OLC capsules groups, respectively.) Overall, 76% compared with 79% of patients and 57% compared with 56% of patients experienced long-term complications of PEG-J and risks of PEG-J insertion in the LCIG + PBO IR OLC capsules group and PBO LCIG + IR OLC capsules group, respectively. The most common long-term complications of PEG-J were complication of device insertion (57% versus 44%), procedural pain (30% versus 35%), and incision-site erythema (19% versus 12%), while the most common risks of PEG-J insertion were abdominal pain (51% versus 32%) and pneumoperitoneum (11% versus 3%) in the LCIG + PBO IR OLC capsules and PBO LCIG + IR OLC capsules groups, respectively.

In general, a similar number of patients (70% compared with 71%) experienced gastrointestinal (GI) AEs, the most common being nausea (30% versus 21%), constipation (22% versus 21%), and flatulence (16% versus 12%) in the LCIG + PBO IR OLC capsules

and PBO LCIG + IR OLC capsules groups, respectively. More patients experienced psychiatric disorders in the LCIG + PBO IR OLC capsules group compared with the PBO LCIG + IR OLC capsules group (46% compared with 29%). The most common were depression (11% versus 3%), insomnia (11% versus 12%), anxiety (8% versus 3%), and confusional state (8% versus 3%) in the LCIG + PBO IR OLC capsules and PBO LCIG + IR OLC capsules groups, respectively. A total of 3% and 9% of patients experienced polyneuropathy and associated signs and symptoms, the most common reason being balance disorder (3% compared with 6%) in the LCIG + PBO IR OLC capsules and PBO LCIG + IR OLC capsules groups, respectively. Fewer patients experienced nervous system disorders in the LCIG + PBO IR OLC capsules group compared with the PBO LCIG + IR OLC capsules group (30% compared with 47%). The most common were dyskinesia (14% versus 12%), dizziness (8% versus 6%), and headache (8% versus 12%) in the LCIG + PBO IR OLC capsules and PBO LCIG + IR OLC capsules groups, respectively. In general, a similar number of patients (22% compared with 27%) experienced vascular disorders, the most common being orthostatic hypotension (14% versus 24%) and hypertension (8% versus 0%) in the LCIG + PBO IR OLC capsules and PBO LCIG + IR OLC capsules groups, respectively.

Generally, AEs (including serious and non-serious) reported in Study 001/002 were consistent with the known AE profile of levodopa/carbidopa (e.g., depression, anxiety, confusion) and PD patients who have undergone the PEG-J procedure.

The primary objectives of Study 003 (N = 62), Study 004 (N = 354), and Study 005 (N = 262) as well as 16 other prospective, open-label, non-comparative trials were to evaluate the long-term safety of LCIG. Overall, the safety profile was generally consistent with that identified in Study 001/002, with no new safety signals identified following up to 60 months of treatment.

Potential Place in Therapy[1]

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

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

the fluctuations can be unpredictable, severe, and have a major impact on patients' abilities to carry out ADL.

A key limitation of oral pharmacological strategies for managing "on" and "off" fluctuations is the suboptimal absorption of the drug from the GI tract. This is particularly problematic for levodopa, which must compete with other small amino acids to gain access to the same small amino-acid transporter in the gastric mucosa in order to pass from the lumen of the stomach into the bloodstream. LCIG alleviates this problem because levodopa is delivered directly to the jejunum by the use of a jejunostomy tube. In addition to improving the reliability of levodopa absorption, the jejunostomy tube allows the patient to absorb levodopa at a more or less constant rate. This implies that levodopa can be delivered to the brain at a relatively constant rate, which is presumed to more closely resemble the normal physiological state. In patients treated with LCIG, it is generally possible to reduce or even discontinue the oral medications the patient was previously receiving.

The patient most likely to benefit from LCIG is one with moderately advanced levodopa-responsive PD (disabled, but ambulatory and at least semi-independent), whose waking hours are characterized by frequent fluctuations between the "on" and "off" states despite receiving optimized therapy with existing drugs. Identification of such patients would be part of routine neurological follow-up. In some centres, where neurosurgical expertise is available, deep brain stimulation might be considered an option in such patients. In some instances, the patient's wishes or general medical condition may make either deep brain stimulation or jejunostomy tube placement impossible, and the only option may be to continue on optimized oral medication. The potential benefits of LCIG would need to be weighed against the inconvenience and potential complications of insertion and living with a jejunostomy tube and infusion pump. The jejunostomy tube insertion requires collaboration with an endoscopist (gastroenterologist or surgeon), implying added cost to the health care system, and follow-up of patients requires some expertise with the maintenance of the infusion pump. Otherwise, the use of Duodopa would not require any new or specific diagnostic testing. At follow-up visits, the patient's functional status would be assessed to ensure that LCIG is still providing benefit. (If in doubt, the infusion rate could be reduced and the impact on function observed directly, usually during a day-long clinic visit.)

Conclusions

A previous CDR review in 2009 of the use of LCIG for PD led to the recommendation by CEDAC that LCIG "not be listed" due to the manufacturer's reported incremental cost per QALY and the limited quality of two trials (open-label design, small sample size, and high proportions of withdrawals, as well as administration through a nasojejunal tube and inclusion of a patient population that was not representative of the target PD population that would be considered for LCIG treatment in Canadian clinical practice).

The CDR systematic review included one double-blind, double-dummy, phase III, active-controlled RCT (Study 001/002) designed to assess the benefits and harms of LCIG compared with IR OLC and one non-comparative, multinational, multi-centre, open-label, long-term safety study (Study 004) designed to assess the harms of LCIG for the treatment of patients with advanced levodopa-responsive PD who do not have satisfactory control of severe, debilitating motor fluctuations and hyper-/dyskinesia despite optimized treatment with available combinations of Parkinson medicinal products, and for whom the benefits of this treatment may outweigh the risks associated with the insertion and long-term use of the PEG-J tube required for administration.

Compared with IR OLC, LCIG was associated with a statistically significant and clinically meaningful reduction in daily normalized “off” time at week 12 (the primary outcome) completed through the PDHD (Study 001/002). Overall, LCIG was also associated with a statistically significant improvement in daily normalized “on” time without troublesome dyskinesia at week 12 (Study 001/002). The results were primarily driven by the increase in “on” time without dyskinesia, whereas the change in “on” time with non-troublesome dyskinesia was not statistically significant. These results continue to support the benefit associated with treatment with LCIG given that the results are being driven by the more desirable component (“on” time without dyskinesia). In general, patients treated with LCIG in Study 004 experienced a significant improvement in daily normalized “off” time and “on” time at week 54 compared with their baselines. The results of other secondary end points adjusted for multiple statistical testing used to assess PD symptoms at week 12 (PDQ-39 summary index score and the UPDRS Part II) were also supportive of the primary analysis, demonstrating statistically significant and clinically meaningful improvement in favour of treatment with LCIG (Study 001/002).

Given that the comparator group in Study 001/002 also included levodopa/carbidopa as a treatment, between-treatment AE differences related to LCIG were not expected. Generally, AEs reported in Study 001/002 were known AEs of levodopa/carbidopa (e.g., depression, anxiety, confusion). Furthermore, the safety profile of the patients treated with LCIG in Study 001/002 was also similar to that of patients with advanced PD who have undergone a PEG-J procedure. The long-term safety of LCIG was explored in Study 003 and Study 005 (both open-label safety extension studies of Study 001/002 and/or Study 004). These studies, in which patients were treated with open-label LCIG for up to 60 months, suggest continued efficacy and no new safety signals compared with baseline.

Table 1: Summary of Efficacy

End Point	Study 001/002 (FAS)		Study 004
	LCIG + PBO IR OLC capsules N = 36	PBO LCIG + IR OLC capsules N = 33	LCIG N = 354
"Off" Time, Hours per Day[ab]			
Baseline, n (%)	35 (97)	31 (94)	316
Baseline, mean (SD)	6.32 (1.72)	6.90 (2.06)	6.75 (2.35)
Adjusted LS mean change from baseline at last study visit (SE)	–4.04 (0.65)	–2.14 (0.66)	–4.4 (2.9), $P < 0.001$[l]
Adjusted LS MD in change from baseline versus comparator (95% CI)	–1.91 (–3.05 to –0.76), $P = 0.0015$		NA
"On" Time Without Troublesome Dyskinesia, Hours per Day[bc]			
Baseline, n (%)	35 (97)	31 (94)	316
Baseline, mean (SD)	8.70 (2.01)	8.04 (2.09)	7.65 (2.45)
Adjusted LS mean change from baseline at last study visit (SE)	4.11 (0.75)	2.24 (0.76)	4.8 (3.4), $P < 0.001$[l]
Adjusted LS MD in change from baseline versus comparator (95% CI)	1.86 (0.56 to 3.17), $P = 0.0059$		NA
PDQ-39 Summary Index Score[cd]			
Baseline, n (%)	36 (100)	33 (100)	320
Baseline, mean (SD)	35.1 (18.0)	38.6 (17.9)	42.8 (15.1)
Adjusted LS mean change from baseline at last study visit (SE)	–10.9 (3.3)	–3.9 (3.2)	–6.9 (14.1), $P < 0.001$[l]
Adjusted LS MD in change from baseline versus comparator (95% CI)	–7.0 (–12.6 to –1.4), $P = 0.0155$		NA
CGI-I Score[et]			
Baseline, n (%)	36 (100)	33 (100)	316
Baseline, mean (SD)[g]	4.2 (0.7)	4.6 (0.8)	4.85 (0.8)
Adjusted LS mean change from baseline at last study visit (SE)	2.3 (0.4)	3.0 (0.4)	NR
Adjusted LS MD in change from baseline versus comparator (95% CI)	–0.7 (–1.4 to –0.1), $P = 0.0258$		NA
UPDRS Part II Score[ch]			
Baseline, n (%)	36 (100)	33 (100)	293
Baseline, mean (SD)	11.6 (6.9)	11.8 (7.0)	17.4 (6.6)
Adjusted LS mean change from baseline at last study visit (SE)	–1.8 (1.3)	1.3 (1.3)	–4.4 (6.5), $P < 0.001$[l]
Adjusted LS MD in change from baseline versus comparator (95% CI)	–3.0 (–5.3 to –0.8), $P = 0.0086$		NA
UPDRS Part III Score[chi]			
Baseline, n (%)	36 (100)	33 (100)	291
Baseline, mean (SD)	18.1 (9.9)	22.5 (11.7)	28.8 (13.7)
Adjusted LS mean change from baseline at last study visit (SE)	–1.5 (2.4)	–2.9 (2.4)	NR
Adjusted LS MD in change from baseline versus comparator (95% CI)	1.4 (–2.8 to 5.6), $P = 0.5020$		NA

End Point	Study 001/002 (FAS)		Study 004
	LCIG + PBO IR OLC capsules N = 36	PBO LCIG + IR OLC capsules N = 33	LCIG N = 354
EQ-5D-3L Summary Index Score[cl]			
Baseline, n (%)	36 (100)	33 (100)	318
Baseline, mean (SD)	0.692 (0.151)	0.617 (0.181)	0.588 (0.195)
Adjusted LS mean change from baseline at last study visit (SE)	0.05 (0.04)	–0.02 (0.04)	0.064 (0.203), $P < 0.001$[l]
Adjusted LS MD in change from baseline versus comparator (95% CI)	0.07 (–0.01 to 0.15), $P = 0.0670$		NA
ZBI Total Score[ck]			
Baseline, n (%)	23 (64)	23 (70)	NR
Baseline, mean (SD)	23.9 (11.6)	23.0 (13.9)	NR
Adjusted LS mean change from baseline at last study visit (SE)	–2.8 (3.7)	1.7 (3.3)	NR
Adjusted LS MD in change from baseline versus comparator (95% CI)	–4.5 (–10.7 to 1.7), $P = 0.1501$		NA

ANCOVA = analysis of covariance; CGI-I = Clinical Global Impression – Improvement; CGI-S = Clinical Global Impression – Severity; CI = confidence interval; CSR = Clinical Study Report; EQ-5D-3L = EuroQol 5-Dimensions 3-Levels questionnaire; FAS = full analysis set; IR = immediate-release; LCIG = levodopa/carbidopa intestinal gel; LOCF = last observation carried forward; LS = least squares; MD = mean difference; NA = not applicable; NR = not reported; OLC = oral levodopa/carbidopa; PBO = placebo; PDQ-39 = 39-itemParkinson's Disease Questionnaire; QoL = quality of life; SD = standard deviation; SE = standard error; UPDRS = Unified Parkinson's Disease Rating Scale; ZBI = Zarit Burden Interview.

Note: All end points are part of the statistical testing hierarchy.

[a] LOCF was used to impute missing data. The normalized totals for the 3 days prior to the visit are averaged for the analysis. Treatment comparisons are based on an ANCOVA model including effects for treatment and country and using the corresponding baseline and the natural logarithm of the mean daily dose of rescue medication on valid symptom diary days as covariates.

[b] The diary is completed every 30 minutes for the full 24 hours of each of 3 days prior to selected clinic visits. It reflects both time awake and time asleep. Daily totals are normalized to a 0-hour to 16-hour scale (i.e., 16 hours of awake time).

[c] Treatment comparisons are based on an ANCOVA model including effects for treatment and country and using the corresponding baseline as covariates.

[d] The PDQ-39 summary index is the sum of all answers divided by the highest score possible (i.e., number of answers multiplied by 4), which is multiplied by 100 to put the score on a 0 to 100 scale. Higher scores are associated with more severe symptoms.

[e] The CGI-I is a global assessment by the investigator of the change in clinical status since the start of treatment. The CGI-I ratings are as follows: 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse. The CGI-S is a global assessment by the investigator of current symptomatology and impact of illness on functioning. The ratings of the CGI-S scale are as follows: 1 = normal, 2 = borderline ill, 3 = mildly ill, 4 = moderately ill, 5 = markedly ill, 6 = severely ill, and 7 = among the most extremely ill.

[f] Treatment comparisons are based on an ANCOVA model including effects for treatment and country and using the CGI-S as a covariate.

[g] Baseline scores are based on the CGI-S score.

[h] Each question is measured on a 5-point scale (0 to 4) where higher scores are associated with more disability. The Part II score is the sum of the answers to the 13 questions that comprise Part II. The Part II score ranges from 0 to 52. The Part III score is the sum of the 27 answers provided to the 14 Part III questions. The Part III score ranges from 0 to 108.

[i] The end point in the statistical testing hierarchy failed prior to the evaluation of this end point.

[j] EQ-5D-3L health states, defined by the EQ-5D-3L descriptive system, are converted into a single summary index by applying a formula that essentially attaches values (also called QoL weights or QoL utilities) to the levels in each dimension.

[k] The ZBI is a 22-item questionnaire regarding the caregiver–patient relationship and evaluates the caregiver's health condition, psychological well-being, finances, and social life. Each question is answered on a 5-point scale where 0 = never, 1 = rarely, 2 = sometimes, 3 = quite frequently, and 4 = nearly always. The caregiver burden is evaluated by the total score (range: 0 to 88) obtained from the sum of the answers to the 22 questions. Higher scores are associated with a higher level of burden for the caregiver.

[l] Unadjusted mean change from baseline at last study visit. Standard deviation instead of standard error. End point not corrected for multiple statistical testing.

Source: Study 001/002 Clinical Study Report,[26] Olanow et al. (2014),[27] Fernandez et al. (2015).[28]

Table 2: Summary of Harms

Harms	Study 001/002 (Safety Set)		Study 004
	LCIG + PBO IR OLC capsules N = 37	PBO LCIG + IR OLC capsules N = 34	LCIG N = 324
AEs			
Patients with > 0 AEs, n (%)	35 (95)	34 (100)	298 (92)
Most common AEs[a]			
Fall	4 (11)	4 (12)	49 (15)
Atelectasis	3 (8)	0	NR (2)
Anxiety	3 (8)	1 (3)	NR
Confusional state	3 (8)	1 (3)	NR
Oedema peripheral	3 (8)	0	NR
Oropharyngeal pain	3 (8)	0	NR
Upper respiratory tract infection	3 (8)	0	NR
Pyrexia	2 (5)	0	NR (2)
Pneumonia	1 (3)	2 (6)	NR (3)
Urinary tract infection	0	4 (12)	37 (11)
SAEs			
Patients with > 0 SAEs, n (%)	5 (14)	7 (21)	105 (32)
Most common SAEs[b]			
Confusional state	2 (5)	0	NR
Pneumonia	0	2 (6)	6 (2)
Complication of device insertion	1 (3)	1 (3)	21 (7)
WDAEs			
WDAEs, n (%)	1 (3)	2 (6)	27 (8)
Most common reasons			
Procedure- or device-related AEs	NR	NR	8 (2)
Complication of device insertion	NR	NR	6 (2)
Abdominal pain	NR	NR	3 (1)
Dyskinesia	NR	NR	2 (1)
Death of unknown etiology	NR	NR	2 (1)
Suicide	NR	NR	2 (1)
Vomiting	NR	NR	1 (< 1)
QT prolongation	NR	NR	1 (< 1)
Anxiety	NR	NR	1 (< 1)
Pneumonia	NR	NR	1 (< 1)
Hallucination	1 (3)	0	1 (< 1)
Psychotic disorder	1 (3)	0	NR
Peritonitis	0	1 (3)	NR
Post-procedural complication	0	1 (3)	NR
Post-procedural discharge	0	1 (3)	NR
Deaths			
Number of deaths, n (%)	0	0	8 (2)
Notable Harms, n (%)			
Device-related complications	**34 (92)**	**29 (85)**	**NR (87)**
Stoma complication	15 (41)	15 (44)	NR

Harms	Study 001/002 (Safety Set)		Study 004
	LCIG + PBO IR OLC capsules N = 37	PBO LCIG + IR OLC capsules N = 34	LCIG N = 324
Intestinal tube complication	14 (38)	12 (35)	NR (51)
PEG-J complication	11 (30)	12 (35)	NR (35)
Pump complication	5 (14)	8 (24)	NR
Pump or stoma complication	NR	NR	NR (36)
Other[c]	17 (46)	13 (38)	
Procedure and device-associated AEs			
Long-term complications of PEG-J	**28 (76)**	**27 (79)**	**NR (69)**
Complication of device insertion	21 (57)	15 (44)	113 (34)
Procedural pain	11 (30)	12 (35)	67 (20)
Incision-site erythema	7 (19)	4 (12)	42 (13)
Post-procedural discharge	4 (11)	3 (9)	NR (8)
Post-operative wound infection	4 (11)	8 (24)	50 (15)
Excessive granulation tissue	2 (5)	0	52 (15)
Procedural-site reaction	2 (5)	2 (6)	NR (9)
Incision-site cellulitis	1 (3)	1 (3)	NR
Medical device site reaction	1 (3)	0	NR
Incision-site complication	0	1 (3)	NR
Post-procedural complication	0	1 (3)	NR
Post-procedural constipation	0	1 (3)	NR
Post-procedural discomfort	0	1 (3)	NR
Post-procedural hemorrhage	0	1 (3)	NR
Post-procedural infection	0	1 (3)	NR
Procedural nausea	0	1 (3)	NR
Incision-site pain	NR	NR	NR (6)
Risk of PEG-J insertion	**21 (57)**	**19 (56)**	**NR**
Abdominal pain	19 (51)	11 (32)	101 (31)
Pneumoperitoneum	4 (11)	1 (3)	NR (6)
Post-operative ileus	2 (5)	0	NR
Abdominal discomfort	1 (3)	3 (9)	NR
Abdominal pain upper	1 (3)	2 (6)	NR
Peritonitis	0	1 (3)	9 (3)
GI AEs	**26 (70)**	**24 (71)**	NR
Nausea	11 (30)	7 (21)	54 (17)
Constipation	8 (22)	7 (21)	47 (15)
Flatulence	6 (16)	4 (12)	NR
Hiatus hernia	3 (8)	2 (6)	NR
Abdominal distension	2 (5)	1 (3)	NR
Diarrhea	2 (5)	1 (3)	NR
Dyspepsia	2 (5)	1 (3)	NR
Vomiting	2 (5)	4 (12)	NR
Gastritis	1 (3)	3 (9)	NR
Mouth ulceration	1 (3)	0	NR
Gastroesophageal reflux disease	0	1 (3)	NR (2)
Peritonitis	0	1 (3)	NR

Harms	Study 001/002 (Safety Set)		Study 004
	LCIG + PBO IR OLC capsules N = 37	PBO LCIG + IR OLC capsules N = 34	LCIG N = 324
Reflux oesophagitis	0	2 (6)	NR
Psychiatric disorders	**17 (46)**	**10 (29)**	NR
Depression	4 (11)	1 (3)	NR
Insomnia	4 (11)	4 (12)	44 (14)
Anxiety	3 (8)	1 (3)	NR (1)
Confusional state	3 (8)	1 (3)	NR
Hallucination	2 (5)	1 (3)	NR
Psychotic disorder	2 (5)	1 (3)	NR
Sleep disorder	2 (5)	0	NR
Delusion	1 (3)	0	NR
Mental status changes	0	1 (3)	NR
Shared psychotic disorder	0	1 (3)	NR
Sleep attacks	0	1 (3)	NR
Polyneuropathy and associated signs and symptoms	**1 (3)**	**3 (9)**	NR (7)
Balance disorder	1 (3)	2 (6)	NR
Asthenia	1 (3)	1 (3)	NR
Hypoesthesia	1 (3)	0	NR
Paresthesia	1 (3)	0	NR
Neuropathy peripheral	0	1 (3)	NR (1)
Speech disorder	0	1 (3)	NR
Nervous system disorders	**11 (30)**	**16 (47)**	NR
Dyskinesia	5 (14)	4 (12)	NR
Dizziness	3 (8)	2 (6)	NR
Headache	3 (8)	4 (12)	NR
Dizziness postural	1 (3)	1 (3)	NR
Freezing phenomenon	1 (3)	2 (6)	NR
Parkinson disease	1 (3)	2 (6)	NR
Neuropathy peripheral	0	1 (3)	NR (1)
Tremor	0	1 (3)	NR
Vascular disorders	**8 (22)**	**9 (27)**	NR
Orthostatic hypotension	5 (14)	8 (24)	NR
Hypertension	3 (8)	0	NR

AE = adverse event; GI = gastrointestinal; IR = immediate-release; LCIG = levodopa/carbidopa intestinal gel; NR = not reported; OLC = oral levodopa/carbidopa; PBO = placebo; PEG- J = percutaneous endoscopic gastrostomy with jejunal extension; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] Frequency > 5%.

[b] Frequency ≥ 5%.

[c] Events that could not clearly be assigned to another specified category based on investigator judgment.

[d] Long-term complication of PEG-J during the 12-week follow-up of Study 001/002.

Source: Study 001/002 Clinical Study Report,[26] Olanow et al. (2014),[27] Fernandez et al. (2015).[28]

Introduction

Disease Prevalence and Incidence

Parkinson disease (PD) is the second most common neurodegenerative disorder after Alzheimer disease.[1] The characteristic features of PD include resting tremor, rigidity, bradykinesia, and postural instability leading to loss of control of voluntary movement.[2-4] The underlying cause of motor symptoms is a combination of chronic degeneration of the dopaminergic neurons in the nigrostriatal region of the brain and depletion of dopamine.[4] Nerve synaptic dysfunction related to the aggregation of alpha-synuclein, a presynaptic protein, and several additional neurotransmitter pathways also play a role in the pathogenesis of PD. [29,30] Further, the progressive loss of dopaminergic neurons results in an inability to store and regulate dopamine function in the brain.[4] Therefore, as PD progresses, impairment in motor functions may worsen over time and can result in debilitating disability. Parkinson disease is also associated with non-motor symptoms, such as neuropsychiatric symptoms, gastrointestinal (GI) symptoms, sleep disturbances, urinary dysfunction, pain, and impulse control disorders.[5,6]

In the early stages of PD, symptoms are typically well controlled with currently available therapies; however, as the disease progresses, therapies become less effective and patients with more advanced PD generally begin to experience more “off” state episodes, in which symptoms of PD re-emerge despite active therapy.[31,32] The manifestation of “off” state episodes typically begins after four to six years of therapy and is a particularly debilitating aspect of the disease characterized by hypomobility, tremor, stiffness, and/or periods of unpredictable immobility.[31,33] Motor fluctuations between the “on” state (when patients are experiencing good medication response and mobility) and “off” state are cardinal features of patients with advanced PD.[7,34]

Non-motor symptoms and motor systems associated with advanced PD are considered troublesome and greatly affect daily routines and the quality of life (QoL) of both patients and their caregivers.[35-43] These symptoms can lead to depression and cognitive impairment, among other detrimental manifestations that can also have a significant impact on the activities of daily living (ADL).[44]

In Canada, PD has a prevalence of approximately 0.5% to 1.0% among adults between 65 years and 69 years of age, rising to 1.0% to 3.0% among those 80 years of age and older.[1,45] Canadian patients typically first experience PD symptoms and are formally diagnosed at a mean of approximately 64 and 66 years of age, respectively. Overall, 79% of patients with PD in Canada are 65 years of age or older. Those who are diagnosed at younger ages are considered to have early-onset PD.[46-48] Generally, the prevalence of PD is greater in men than in women (0.3% compared with 0.2%, respectively) and increases with age (occurring in 2.1% compared with 1.0% of adults 80 years of age or older, respectively).[46-48] Based on data derived from the Canadian Microsimulation Project, over the next 20 years, it is estimated that the number of Canadians living with PD will nearly double and that incidence rate will increase by 50% between 2016 and 2031 (from 60 per 100,000 to 90 per 100,000, respectively). Furthermore, deaths attributed to PD are expected to increase by 74% by 2031.[48]

Standards of Therapy

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

A number of dopaminergic antiparkinsonian medications are marketed worldwide and in Canada. Levodopa, a precursor of dopamine, is the first-line treatment due to its effectiveness in minimizing motor-related PD symptoms, including tremor, rigidity, and bradykinesia, by restoring dopamine deficiency at the nigrostriatal region in the brain.[7] The Canadian Guidelines on Parkinson Disease recommend that oral levodopa be given in combination with any of the following based on PD stage and tolerability: in fixed combination with dopa decarboxylase inhibitors (carbidopa or benserazide), monoamine oxidase type B (MAO-B) inhibitors (selegiline and rasagiline), or anticholinergics (trihexyphenidyl and procyclidine); or in fixed combination with carbidopa and entacapone, a catechol-O-methyltransferase (COMT) inhibitor.[7] These adjunct drugs prevent the rapid metabolism of levodopa into dopamine, whose short plasma half-life (1.5 hours) improves the bioavailability of levodopa and reduces the peripheral side effects associated with levodopa treatment, such as nausea and vomiting. The most common early side effects associated with levodopa include nausea, somnolence, dizziness, and headache. Long-term administration may lead to confusion, hallucinations, delusions, agitation, psychosis, and orthostatic hypotension, particularly in older patients.[8]

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

Intermittent treatment with oral levodopa/carbidopa (OLC) can result in fluctuating plasma concentrations due to erratic gastric emptying, variable jejunal absorption, and the short half-life of the drug.[49,50] Furthermore, given that PD is degenerative (leading to reduced capacity to store and regulate dopamine), the long-term efficacy of OLC in most patients is reduced, causing patients to require more frequent dosing regimens and leading to more episodes of "off" and "on" states. Both of these factors contribute to the fluctuations between "off" and "on" states, leading to unsatisfactory control of symptoms.[2,27]

Despite the efficacy of levodopa for most PD patients, some continue to develop motor complications that can persist for a significant portion of the waking day. The controlled-release formulation of levodopa/carbidopa is often offered in more severe cases to manage

motor fluctuations and “wearing-off” episodes; however, this treatment is limited by potential erratic absorption and delayed response.[8] Other types of drugs can be administered as an adjunct to levodopa in an attempt to reduce “off” time.[8] MAO-B inhibitors, such as rasagiline and selegiline, prevent the metabolism of dopamine in the brain, while COMT inhibitors, such as entacapone, increase the bioavailability of levodopa in the periphery.[7] Anticholinergics, such as trihexyphenidyl and benztropine, are mostly used in patients with tremor and in hard-to-treat patients; however, neuropsychiatric side effects limit their use in older patients.[7] Treatment for advanced PD can also include apomorphine hydrochloride (a potent post-synaptic dopamine agonist), which is approved for the treatment of acute, intermittent hypomobility “off” episodes (“end-of-dose wearing off” and unpredictable “on/off”) in patients with advanced PD.

A more invasive option reserved for patients with advanced PD who are inadequately managed despite optimized standard therapies is deep brain stimulation (DBS), a stereotactic brain surgery that involves implanting a pacemaker-like device that sends electrical pulses to the brain in hopes of blocking nerve signals that cause PD symptoms in order to help improve “off” time and dyskinesia. [51,52] Generally, DBS is only done at specialized centres in Canada and requires a specialized team of neurologists, neurosurgeons, technicians, and nurses. DBS therapy has been shown to be highly effective at controlling motor complications; however, very few patients are considered candidates for this procedure since patients older than 70 years of age with moderate to severe depression or cognitive decline are considered poor candidates.[51] Despite its efficacy, it is important to note that DBS surgery only improves the motor symptoms, and that non-motor symptoms (i.e., dementia, swallowing difficulties, poor balance) also cause significant disability for many individuals with advanced PD. Furthermore, although DBS is considered particularly effective in relieving motor symptoms, it does carry significant risk (of death or major stroke) and is generally not performed in older patients or those with neuropsychiatric disorders.[51,52]

Drug

Levodopa is a metabolic precursor of dopamine used to relieve the motor symptoms of PD. It is transported across the blood-brain barrier and subsequently decarboxylated into dopamine. Levodopa is often given in combination with carbidopa, which is used to inhibit the peripheral decarboxylation of levodopa, subsequently increasing its bioavailability. Therefore, combination therapy with levodopa/carbidopa reduces the amount of levodopa required for optimum therapeutic benefit and minimizes the incidence of AEs attributed to high levels of peripheral dopamine, such as nausea, vomiting, and cardiac arrhythmias.[9] Duodopa is a levodopa/carbidopa intestinal gel (LCIG) formulation that is infused directly into the proximal small intestine. It is intended to mitigate the influences on the absorption rate of intermittent OLC dosing and unpredictable gastric emptying associated with PD by providing relatively constant plasma concentrations of levodopa.[9]

Treatment with LCIG is intended for long-term administration. The LCIG is infused using a portable CADD-Legacy Duodopa pump. It goes directly into the duodenum or upper jejunum through a percutaneous endoscopic gastrostomy with jejunal extension (PEG-J) tube comprised of an outer transabdominal tube and an inner intestinal tube. However, prior to permanent PEG-J tube placement, short-term treatment through a nasojejunal (NJ) tube is recommended in all patients. Furthermore, patient response, ability to tolerate the device and drug, and ability to manage the daily operations of the device should be assessed prior to tube placement. [9]

According to the Health Canada–approved indication, LCIG can be used for the treatment of patients with advanced levodopa-responsive PD who do not have satisfactory control of severe, debilitating motor fluctuations and hyper-/dyskinesia despite optimized treatment with available combinations of PD medicinal products, and for whom the benefits of this treatment may outweigh the risks associated with the insertion and long-term use of the PEG-J tube required for administration.[9]

LCIG dosing should be individualized for each patient and adjusted for optimal clinical response, defined as maximizing functional "on" time during the day, and by minimizing the number and duration of "off" episodes (bradykinesia) in addition to minimizing "on" time with disabling dyskinesia. Patients receive training (on administration of treatment, PEG-J use, and pump care). Doses are individualized during the NJ test period. In addition, patients are able to independently adjust their infusion rates to suit their daily requirements within parameters specified by a physician.[9] Treatment is administered over approximately 16 hours and is composed of three individually adjusted doses: the morning bolus dose, the continuous maintenance dose, and extra bolus doses.[9] The LCIG (20 mg/mL levodopa and 5 mg/mL carbidopa monohydrate solution) is packaged in a 100 mL cassette containing 2,000 mg levodopa and 500 mg carbidopa. The cassettes are for single use only and should not be reused once opened. In addition, a single cassette should not be used for longer than 16 hours despite the possibility of medicinal product remaining.[9]

The morning dose is initially administered at between 60% and 80% of OLC doses (depending on the usual OLC morning dose) to achieve a therapeutic level within 10 minutes to 30 minutes, and usually corresponds to about 5 mL to 15 mL (equivalent to 100 mg to 300 mg of levodopa). An additional 3 mL should be added to compensate for priming of the empty space in the tubing. Once an effective dose has been established, no further adjustments to the morning dose should be made.[9] The continuous maintenance dose is administered over a 16-hour waking day based on a calculation: the previous day's dose minus the morning dose = A mg; divide A mg by 20 mg/mL = B mL; divide B mL by 16 hours = C mL/hour; C x 0.9 = D mL/hour rate of infusion. It can be adjusted in increments of 0.1 mL/hour (equivalent to 2 mg/hour of levodopa), with typical doses ranging between 1 mL/hour and 10 mL/hour (equivalent to 20 mg/hour to 200 mg/hour of levodopa). Once an effective dose has been established, no further adjustments to the morning dose should be made.[9] The extra bolus doses are self-administered and can be used to address immediate medical needs, such as the rapid deterioration of motor function (e.g., patient becomes hypokinetic) at a rate of 0.5 mL/hour to 2.0 mL/hour during the titration period and at a rate of 0.5 mL to 2.0 mL every two hours thereafter. If the extra bolus doses exceed five doses per day, an increase in the continuous maintenance dose should be considered. The PEG-J tube is to be disconnected from the pump at bedtime and flushed with room-temperature potable water as a preventive measure against occlusions. Patients should be initially treated with LCIG as a monotherapy; however, concomitant treatment with other therapies for PD can be considered if required.[9]

Contraindications for treatment with LCIG include hypersensitivity to any ingredient in the formulation or component of the container; narrow-angle glaucoma; suspicious, undiagnosed skin lesions or a history of melanoma; and clinical or laboratory evidence of uncompensated cardiovascular, cerebrovascular, endocrine, renal, hepatic, hematologic, or pulmonary disease (including bronchial asthma). Concomitant use of nonselective MAO inhibitors and selective MAO type A inhibitors are also contraindicated. Treatment with LCIG should not be administered when sympathomimetic amines are contraindicated (e.g., epinephrine, norepinephrine, isoproterenol).

The placement of a PEG-J tube is contraindicated in patients with pathological changes of the gastric wall, inability to bring the gastric wall and abdominal wall together, blood coagulation disorders, peritonitis, acute pancreatitis, and paralytic ileus.

Table 3: Key Characteristics of Parkinson Disease Therapies

	Rotigotine	Ropinirole	Pramipexole	Levodopa/carbidopa	Levodopa/benserazide	LCIG
Mechanism of Action	Non-ergolinic dopamine agonist; it is believed to reduce the symptoms of Parkinson disease by increasing the activities of the D3, D2, and D1 receptors of the caudate putamen in the brain, but is an agonist for D1-D5 receptors.	Non-ergolinic dopamine agonist; activates post-synaptic dopamine receptors.	Non-ergolinic dopamine agonist with high in vitro specificity at the D2 subfamily of dopamine receptors.	Levodopa crosses the blood-brain barrier and is converted into dopamine in the basal ganglia. Carbidopa is a decarboxylase inhibitor limited to peripheral tissues; it makes more levodopa available for transport to the brain.	Levodopa crosses the blood-brain barrier and is converted to dopamine in the basal ganglia. Benserazide is a decarboxylase inhibitor limited to peripheral tissues; it makes more levodopa available for transport to the brain.	Levodopa crosses the blood-brain barrier and is converted to dopamine in the basal ganglia. Carbidopa is a decarboxylase inhibitor limited to peripheral tissues; it makes more levodopa available for transport to the brain.
Indication[a]	Treatment of the signs and symptoms of idiopathic Parkinson disease. Can be used both as early therapy without concomitant levodopa and as an adjunct to levodopa.			Treatment of Parkinson disease	Treatment of Parkinson's disease with the exception of drug-induced parkinsonism	Treatment of patients with advanced levodopa-responsive Parkinson disease who do not have satisfactory control of severe, debilitating motor fluctuations and hyper-/dyskinesia despite optimized treatment with available combinations of PD medicinal products, and for whom the benefits of this treatment may outweigh the risks associated with the insertion and long-term use of the PEG-J tube required for administration.
Route of Administration	Transdermal	Oral				Intestinal infusion through a PEG-J tube.
Recommended Dose	Transdermal system 2 mg/24h, 4 mg/24h, 6 mg/24h, 8 mg/24h rotigotine[b] The recommended starting dose for PD is 2 mg/24 hours, with	Tablets 0.25 mg, 0.5 mg, 1.0 mg, 2.0 mg, 3.0 mg, 4.0 mg, 5.0 mg The recommended	Tablets 0.125 mg, 0.25 mg, 0.5 mg, 1.0 mg, 1.5 mg The maximal	Immediate-release tablets: 100 mg/10 mg; 100 mg/25 mg; 250 mg /25 mg (initial dosage for patients currently treated with levodopa alone or patients without prior levodopa therapy)	Capsules: 50 mg/12.5mg, 100 mg/ 25 mg/200 mg/ 50 mg The initial recommended dose is one capsule of PROLOPA 100-25 once or twice a day.	The morning dose is initially administered at between 60% and 80% of OLC doses (depending on the usual morning dose) and usually corresponds to about 5 mL to 15 mL (equivalent to 100 mg to 300 mg of levodopa). An

	Rotigotine	Ropinirole	Pramipexole	Levodopa/carbidopa	Levodopa/benserazide	LCIG
	increases in 2 mg increments per week as needed; the maximal dose is 8 mg/24h for early PD, and 16 mg/24h for advanced PD.	maximum dose is not explicitly identified under dosage, but referred to in retinal pathology animals studies as 24 mg/day. Doses greater than 24 mg/day have not been included in clinical trials. In clinical trials, initial benefits were observed with 3 mg/day and higher doses. The recommended maximum dose is 18 mg/day in patients receiving regular dialysis.	recommended dose is 4.5 mg per day.	Controlled-release tablets: 200 mg/50 mg (initial dosage for patients currently treated with levodopa alone) 100 mg/25 mg (patients without prior levodopa therapy)		additional 3 mL should be added to compensate for priming of the empty space in the tubing. The continuous maintenance dose is administered of a 16-hour waking day based on a calculation (previous day's dose minus morning dose = A mg; divide A mg by 20 mg/mL = B mL; divide B mL by 16 hours = C mL/hour; C × 0.9 = D mL/hour rate of infusion) and can be adjusted in increments of 0.1 mL/hour (equivalent to 2 mg/hour of levodopa), with typical doses ranging between 1 mL/hour and 10 mL/hour (equivalent to 20 mg/hour to 200 mg/hour of levodopa). The extra bolus doses are self-administered and can be used to address immediate medical needs, such as the rapid deterioration of motor function (e.g., patient becomes hypokinetic) at a rate of 0.5 mL/hour to 2.0 mL/hour during the titration period and at a rate of 0.5 mL to 2.0 mL every two hours thereafter. If the extra bolus doses exceed 5 doses/day, an increase in the continuous maintenance dose should be considered.

	Rotigotine	Ropinirole	Pramipexole	Levodopa/carbidopa	Levodopa/benserazide	LCIG
Safety Issues	**Contraindications:** Hypersensitivity to rotigotine or excipients **Serious W & P**: Sudden onset of sleep **W & P**: Elevation of blood pressure and heart rate, orthostatic hypotension, fluid retention and weight gain, fibrotic complications (includes cardiac; unknown if non-ergot dopamine agonists cause this as well as ergot dopamine agonists), sulfite sensitivity, restless leg syndrome augmentation or rebound, neuroleptic malignant syndrome (sudden discontinuation), dyskinesia, hallucinations/abnormal thinking and behaviour, impulse control disorders, retinal degeneration (preclinical), application site reactions, melanoma Geriatrics: similar plasma concentrations in age 65 to 80 versus age 50 to 64; absorption in age > 80 years not studied, but may be higher due to skin	*Similar to rotigotine* **W & P** (additional): rhabdomyolysis (a single case excreted through kidneys), caution if renal insufficiency 25% to 30%, lower total clearance in age 65; no difference in AE reported	*Similar to rotigotine*	**Contraindications:** hypersensitivity, concomitant sympathomimetic drug is contraindicated, use of nonselective monoamine oxidase inhibitors, narrow-angle glaucoma, uncompensated cardiovascular, endocrine, renal, hepatic, hematologic, or pulmonary disease; levodopa may activate malignant melanoma, should not be used if suspicious undiagnosed skin lesions or history of melanoma **Serious W & P:** Sudden onset of sleep **W & P:** Cardiovascular: atrial, nodal or ventricular arrhythmias or history of myocardial infarction; upper GI hemorrhage with history of peptic ulcer disease. Neurologic: involuntary movements and “on and off” phenomena may appear earlier in combination with carbidopa; involuntary	*Similar to levodopa/carbidopa*	*Similar to levodopa/carbidopa* **Contraindications**: (additional): The placement of a PEG-J tube is contraindicated in patients with pathological changes of the gastric wall, inability to bring the gastric wall and abdominal wall together, blood coagulation disorders, peritonitis, acute pancreatitis, and paralytic ileus. **Serious W & P:** (additional): Procedure- and device-related complications The morbidity and mortality associated with the procedure used for placing the PEG-J and long-term use of PEG-J need to be balanced against the expected benefits of using LCIG.

	Rotigotine	Ropinirole	Pramipexole	Levodopa/carbidopa	Levodopa/benserazide	LCIG
	changes with aging.			movements and mental disturbances; dyskinesias may occur at lower dosages and sooner in combination with carbidopa; neuroleptic malignant syndrome; psychomotor performance (somnolence, sudden onset of sleep). Psychiatric: monitor for development of depression with suicidal tendencies; treat with caution if past or current psychoses; impulse control disorders; hallucinations; melanoma.		

AE = adverse event; GI = gastrointestinal; LCIG = levodopa/carbidopa intestinal gel; OLC = oral levodopa/carbidopa; PD = Parkinson disease; PEG-J = percutaneous endoscopic gastrostomy-jejunostomy; W & P = warnings and precautions.

Note: The potential for retinal degeneration is based on a similar mechanism between humans and the preclinical model.

[a] Health Canada indication.

[b] Rotigotine transdermal patches are also available in nominal doses of 1 mg and 3 mg for idiopathic restless legs syndrome.

Source: Health Canada product monographs.[53-58]

Submission History

In July, 2009, CEDAC issued a recommendation that Duodopa be "not listed."[59] Key reasons for the recommendation included:

- The manufacturer's reported incremental cost per quality-adjusted life-year (QALY) estimate for Duodopa of [redacted] to [redacted] compared with conventional oral drug therapies. The manufacturer requested that specific results from the economic evaluation remain confidential pursuant to the CADTH Common Drug Review (CDR) confidentiality guidelines. Other published cost per QALY estimates for Duodopa were reported at approximately $1 million dollars.
- The quality of two trials considered by the Committee was limited by open-label designs, high proportions of withdrawals in trials of small sample size, and patient populations that are not representative of those who are most likely to use Duodopa. Therefore, given concerns with the quality of these trials, the relevance of the results was limited.

Summary of Committee Considerations: [59]

The Committee considered the results of a systematic review that included two randomized, open-label crossover trials evaluating the effects of Duodopa in patients with advanced PD and severe motor complications. The DIREQT trial (n = 25) compared Duodopa with patients' pre-study conventional therapies. Treatment sequences were three weeks. The primary outcomes in the DIREQT trial were Unified Parkinson Disease Rating Scale (UPDRS) item scores and time spent in various motor states as assessed by video recording. QoL was also measured in the DIREQT trial. In the NPP-001-99 trial (n = 16), Duodopa was compared with long-acting levodopa/carbidopa, and the short-acting formulation was given to patients as needed. Long-acting levodopa/carbidopa is not considered an appropriate comparator in this patient population.

The validity of results from the two trials was limited by a number of factors, including open-label designs and high proportions of withdrawals in trials of small sample size. Furthermore, the generalizability of the study conclusions is limited because the patient populations included are not representative of those most likely to use Duodopa. It is likely that patients using Duodopa will be over age 70; i.e., those who do not qualify for DBS. However, these trials were conducted in a younger population with an average age ranging from 60 years to 68 years across trials and treatment groups. In both studies, Duodopa was administered by a nasoduodenal tube rather than by the intended PEG-J tube associated with the marketed product. It is not clear if the effect would be similar for nasoduodenal and PEG-J administration. Therefore, given concerns with trial quality, the relevance of the results was limited.

In the DIREQT trial, there were statistically significant improvements in QoL, UPDRS scores (range: 0 to 199), and motor function with Duodopa compared with conventional drug therapy. QoL, measured by the 39-item Parkinson's Disease Questionnaire (PDQ-39) (range: 0 to 100), was statistically significantly improved with Duodopa compared with conventional treatment (median difference = -9.0, $P < 0.01$). Motor function, measured as the percentage of "on" time during video recording, was statistically significantly higher with Duodopa compared with conventional treatment [median difference (range) = 4.5% (–14.7 to 63.2; $P < 0.01$)]. The percentage of "off" time was statistically significantly lower with Duodopa compared with conventional drug therapy (median difference = –8.1%, $P < 0.01$). The magnitude of between-treatment differences for all measures was considered clinically

important. However, the lack of blinding and the use of per-protocol analysis for most outcomes may have biased estimates of efficacy in favour of Duodopa.

The proportions of patients experiencing serious adverse events (SAEs) and AEs were similar between treatment groups in both studies. Common AEs included well-documented effects of levodopa/carbidopa involving the GI tract (i.e., constipation, diarrhea) and the central nervous system (i.e., depression, insomnia, somnolence), as well as administration-related complications (dislocated tubes and intolerance to or dislike of the nasoduodenal tube or pump). Withdrawal due to an AE occurred in three Duodopa patients and no patients in the conventional treatment group in the DIREQT trial.

The Committee also noted the results of two small (n = 13 and n = 22) uncontrolled studies with a pre-post design that provided clinical inputs for the manufacturer's economic evaluation. Results were reported over time periods ranging from six months to two years. Statistically significant improvements were observed for only subjective patient-reported outcomes, such as QoL, ADL, and motor function (measured as "off" and "on" time). There were no statistically significant improvements in clinician-assessed motor function as measured by the UPDRS. The validity of these studies is limited due to their lack of control groups and reliance on observed case analysis when data were missing.

In the cost-utility analysis submitted by the manufacturer, Duodopa was compared with conventional oral drug therapies (i.e., levodopa/carbidopa, cabergoline, pramipexole, pergolide, entacapone, amantadine sulphate, and/or selegiline) for the treatment of advanced PD over a five-year period. The manufacturer's results were highly dependent on the study selected to inform the clinical input parameters, with the manufacturer reporting incremental cost per QALY estimates for Duodopa ranging from approximately [redacted] to [redacted]. The manufacturer requested that specific results from the economic evaluation remain confidential pursuant to the CDR confidentiality guidelines. The cost of Duodopa is $166 per day; in comparison, oral forms of levodopa/carbidopa cost less than $3 per day.

Basis of Resubmission

The basis of the resubmission, as indicated by the Drug Policy Advisory Committee Formulary Working Group (DPAC-FWG), is the new clinical information (systematic reviews, randomized controlled trials [RCTs], and observational studies) that has been available for the treatment of PD with LCIG since the original CDR review in 2009. The CDR-participating drug plans expressed the need for an updated review of the best available evidence and a formulary reimbursement recommendation from the CADTH Canadian Drug Expert Committee (CDEC) to address the use of LCIG for the treatment of PD. In response to DPAC-FWG formally requesting the manufacturer of LCIG (AbbVie Corporation) to file a resubmission for the review of LCIG through the CDR process, the manufacturer indicated that it did not plan to file a CDR resubmission for LCIG. Therefore, DPAC-FWG requested that CADTH undertake a review of LCIG through the CDR process. The CDR-participating drug plans submitted a resubmission for the review of LCIG (Duodopa) for the following Health Canada–approved indication:

For the treatment of patients with advanced levodopa-responsive PD:

- who do not have satisfactory control of severe, debilitating motor fluctuations and hyper-/dyskinesia despite optimized treatment with available combinations of PD medicinal products, and

- for whom the benefits of this treatment may outweigh the risks associated with the insertion and long-term use of the PEG-J tube required for administration.

The original CDR review of Duodopa in 2009 was based on the following Health Canada–approved indication: for the treatment of advanced levodopa-responsive PD in which satisfactory control of severe, disabling motor fluctuations and hyper-/dyskinesia cannot be achieved with available combinations of PD medicinal products.

An early-stage clinical development program for Duodopa (LCIG) provided preliminary efficacy and safety data (based on the DIREQT and NPP-001-99 trials) for the initial conditional marketing authorization of this product (i.e., Notice of Compliance with conditions) pending additional evidence, including the results of a 12-week, double-blind (DB) RCT where Duodopa was administered through a PEG-J tube. The conditions have since been removed based on the Duodopa phase III Clinical Development Program (Study 001/002 and Study 004) conducted subsequent to conditional marketing authorization to confirm the preliminary findings of the early-stage clinical development program.

Objectives and Methods

Objectives

To perform a systematic review of the beneficial and harmful effects of LCIG for continuous intestinal infusion administered as per Health Canada–approved dose for the treatment of advanced levodopa-responsive PD in patients who do not have satisfactory control of severe, debilitating motor fluctuations and hyper-/dyskinesia despite optimized treatment with available combinations of PD medicinal products, and for whom the benefits of this treatment may outweigh the risks associated with the insertion and long-term use of the PEG-J tube required for administration.

Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review, as well as those meeting the selection criteria presented in Table 4.

Any studies included in the previous CDR review (2009) were not included in the body of new evidence summarized in the current review.

Table 4: Inclusion Criteria for the Systematic Review

Patient Population	Patients with advanced levodopa-responsive Parkinson disease who do not have satisfactory control of severe, debilitating motor fluctuations and hyper-/dyskinesia despite optimized treatment with available combinations of PD medicinal products, and for whom the benefits of this treatment may outweigh the risks associated with the insertion and long-term use of the PEG-J tube required for administration. **Subgroups:** • Age • Baseline severity of PD • Duration of PD • Baseline concomitant medications for PD
Intervention	Levodopa/carbidopa intestinal gel[a] (through a PEG-J tube), alone or in combination with other PD therapies
Comparators	Standard pharmacotherapy, which may include: • Oral levodopa/dopa decarboxylase inhibitor • Dopamine agonist • MAO-B inhibitor • COMT inhibitor • Apomorphine Placebo Deep brain stimulation
Outcomes	**Key efficacy outcomes:** • Mobility[b] (or hypomobility) • Time in “off,” “on,” and “on with dyskinesia” states[c] • Frequency of “off” events[c] • Dyskinesia*[b] (frequency and severity) • Time to response (interval between administration and declared recovery)[c] • Functional capacity (work, leisure, ADL)[b,c] • Health-related quality of life[b,c] • Hospitalization • Surgical and infusion complications (e.g., abdominal pain, bezoar, ileus, implant site erosion/ulcer, intestinal hemorrhage, intestinal ischemia, intestinal obstruction, intestinal perforation, intussusception, pancreatitis, peritonitis, pneumoperitoneum, post-operative wound infection, tube dislocation)

Outcomes	**Other efficacy outcomes:** • Use of other PD medications • Use of health care services **Harms outcomes:** • AEs • SAEs • WDAEs • Mortality • Notable harms: fatigue,[c] somnolence, drowsiness,[c] dizziness, headache, symptomatic orthostatism, dyskinesia,[c] dystonia,[c] neuropathy, impulse control disorders, mental changes, depression with suicidal tendencies, neuroleptic malignant syndrome, confusion, hallucinations, delusions, agitation, psychosis, GI adverse events, carcinogenicity, orthostatic hypotension

ADL = activities of daily living; AE = adverse event; CDR = CADTH Common Drug Review; COMT = catechol-0-methyltransferase; GI = gastrointestinal; MAO-B = monoamine oxidase type B; PD = Parkinson disease; PEG-J = percutaneous endoscopic gastrostomy-jejunostomy; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] Administered as per Health Canada–approved product monograph. Morning dose: usually 5 mL to 10 mL, corresponding to 100 mg to 200 mg levodopa, and will normally not exceed 15 mL (300 mg levodopa). The calculated morning dose should be increased by 3 mL to compensate for the priming of the dead space. Continuous maintenance dose: may range from 1 mL/hour to 10 mL/hour (20 mg to 200 mg levodopa/hour) and is usually 2 mL/hour to 6 mL/hour (40 mg to 120 mg levodopa/hour). In exceptional cases, a higher dose may be needed. Extra doses: usually 0.5 mL to 2.0 mL. In rare cases, a higher dose may be needed. If the need for extra doses exceeds five doses per day, the physician should consider increasing the maintenance dose.

[b] Based on validated measures.

[c] Identified as an important outcome in the patient group input submission to CDR.

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

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

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on February 12, 2018. Regular alerts were established to update the search until the CDEC meeting on July 12, 2018. Regular search updates were performed on databases that do not provide alert services.

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

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 one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 5; excluded studies (with reasons) are presented in Appendix 3.

Results

Findings from the Literature

A total of 20 studies were identified from the literature for inclusion in the systematic review (Figure 1). The studies deemed pivotal by the manufacturer are summarized in Table 5. A list of excluded studies is presented in Appendix 3.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

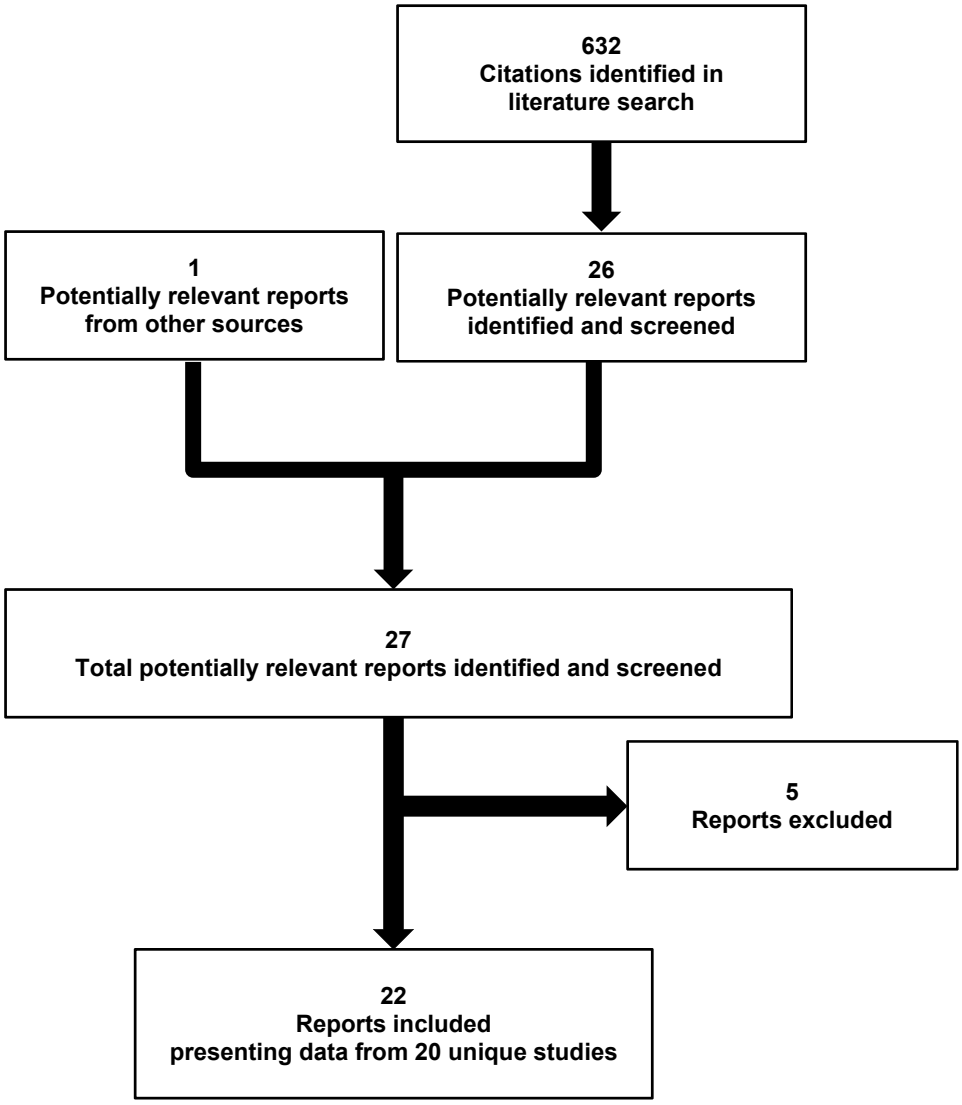


Table 5: Details of Included Studies

		Study 001/002	Study 004
Designs & Populations	**Study Design**	DB, double-dummy, multi-centre, multinational, active-controlled, phase III RCT	Open-label, non-comparative, multi-centre, multinational, long-term safety study
	Locations	26 centres in the US, Germany, and New Zealand	86 centres in 16 countries (including Canada)
	Randomized (N)	71	354
	Inclusion Criteria	Levodopa-responsive adults ≥ 30 years of age[a] Advanced Parkinson disease consistent with UK Brain Bank criteria complicated by "off" periods that could not be satisfactorily controlled with optimized medical therapy.[b] Patients must have received stable doses of levodopa for a minimum of 4 weeks before study enrolment. Patients' histories of antiparkinsonian therapy included the following:[c] • Demonstrated a significant response to levodopa • Adequate trial of IR levodopa/decarboxylase inhibitor or controlled-release levodopa/decarboxylase inhibitor administered at a daily dose equivalent to ≥ 400 mg levodopa • Adequate trial of a dopaminergic agonist administered concomitantly with levodopa/decarboxylase inhibitor • Adequate trial of a COMT inhibitor or MAO-B inhibitor. Concomitant antiparkinsonian drugs (other than apomorphine) were permitted if patients were on stable doses for 4 weeks prior to randomization and doses were not changed during the study. Recognizable "off" and "on" state (motor fluctuations), as confirmed by PD diary recordings prior to the PEG-J procedure. Minimum of 3 hours of "off" time confirmed by PD diary for each of 3 consecutive days prior to the PEG-J procedure (mostly during a continuous 16-hour interval in which the patient was awake). Patient or caregiver was able to complete both the daily dosing diary and the PD diary for recording "off" time and operate, manipulate, and care for the infusion pump and tubing.	Patients ≥ 30 years of age who were levodopa-responsive meeting the UK Parkinson's Disease Society Brain Bank diagnostic criteria. Patients were required to have severe motor fluctuations, defined as ≥ 3 hours of daily "off" time at baseline (confirmed through PD diary), despite currently available optimized PD therapies.

		Study 001/002	Study 004
		Patient's PD diary was 75% compliant for completion and 75% in agreement with the investigator's or qualified designee's assessment of symptoms following training. Patient was suitable for treatment with LCIG, including PEG-J placement, as attested by an independent physician.	
	Exclusion Criteria	Atypical or secondary parkinsonism, Parkinson-plus syndromes, or other neurodegenerative diseases. Previous neurosurgical treatment for Parkinson disease. Any neurological deficit that could interfere with the study assessments, or acute stroke diagnosed within the 6 months prior to randomization. Patient experienced sleep attacks or was exhibiting clinically significant impulsive behaviour (i.e., pathological gambling or hypersexuality) at any point during the 3 months prior to the screening evaluation. Patient had psychiatric, neurological, or behavioural disorders that could have interfered with the ability to give informed consent or with conduct or interpretation of the study. Uncontrolled hallucinations with permitted concomitant therapies. Significant cognitive impairment that, in the opinion of the investigator, would have affected the patient's ability to participate in the trial (e.g., MMSE status score of < 24, Alzheimer disease, or other dementia). Patients who were likely to not have completed the study or had an uncooperative attitude or reasonable likelihood of non-compliance with the protocol, study procedures, or treatments, as per investigator judgment. Malignant disease within the past 5 years prior to screening. Planned surgical procedure scheduled during the study. Exposure to any investigational drug within 30 days prior to day 1 of the study.	NR

		Study 001/002	Study 004
		Prior exposure to LCIG. Laboratory abnormalities in the judgment of the investigator, or any current conditions or history of conditions that might interfere with absorption, distribution, metabolism, excretion, or the assessment of the safety of the study drug or insertion of the PEG-J tube. Known hypersensitivity or contraindications (e.g., narrow-angle glaucoma, pheochromocytoma, Cushing's syndrome, or history of malignant melanoma) to levodopa, carbidopa, or radiopaque material. Current substance abuse or history of substance abuse within 12 months prior to randomization. Patients for whom the placement of a PEG-J tube for LCIG treatment was contraindicated or who were considered a high risk for the PEG-J procedure, according to the gastroenterologist's evaluation.[d]	
Drugs	**Intervention**	LCIG through a PEG- J tube (20 mg/mL levodopa and 5 mg/mL carbidopa monohydrate solution) in 100 mL cassettes in combination with matched placebo IR OLC capsules. Administered as a morning bolus (ranged between 5 mL and15 mL [100 mg to 300 mg levodopa] over 10 minutes to 30 minutes to achieve therapeutic dose levels; additional 3 mL was to be added to the morning dose each day to allow for the priming of the PEG-J tubing) followed by continuous infusion at a constant rate for the remainder of each patient's waking day (approximately 16 hours) through a PEG-J tube (ranged between 1 mL/hour and 10 mL/hour [20 mg/hour to 200 mg/hour levodopa]).	LCIG as a homogenous suspension of levodopa (20mg/mL) and carbidopa monohydrate (5mg/mL) in an aqueous gel (sodium carboxymethyl cellulose) administered as a morning dose/bolus followed by continuous (through the waking day, approximately 16 hours) infusion through a portable pump device with dosing based on patients' previous dose of daily oral levodopa.
	Comparator(s)	IR OLC capsules (100 mg levodopa and 25 mg carbidopa) in combination with matched placebo LCIG gel through a PEG-J tube (sodium carboxymethylcellulose solution alone) were initially administered in divided doses over the course of each patient's waking day (approximately 16 hours) beginning at the same time as the infusion and at the same dose and frequency as at baseline.	None

		Study 001/002	Study 004
Duration	**Phase**		
	Screening	Up to 28 days	Up to 28 days
	Hospitalization	10 days	NR
	Titration	4 weeks	2 days to 14 days[f]
	Maintenance	8 weeks	54 weeks
Outcomes	**Primary End Point**	Change from baseline to final visit (week 12) in the daily normalized "off" hours[e]	Safety assessed through AEs, infusion device complications, and number of completers
	Secondary End Points	**Key secondary end points** "On" time without troublesome dyskinesia ("on" time without dyskinesia and "on" time with non-troublesome dyskinesia). **Other secondary end points** • Change from baseline in PDQ-39 summary index score at week 12 • CGI-I score at week 12 • Change from baseline in UPDRS Part II score at week 12 • Change from baseline in UPDRS Part III score at week 12 • Change from baseline in EQ-5D-3L summary index score at week 12 • Change from baseline in ZBI total score at week 12	**Efficacy:** • Change from baseline in "off" time" • Change from baseline in "on" without troublesome dyskinesia • Change from baseline in "on" with troublesome dyskinesia • Change from baseline in UPDRS **Health-related QoL:** • PDQ-39 • EQ-5D-3L • EQ VAS • CGI-I
Notes	**Publications**	Olanow et al. (2014)[27] Hirsch et al. (2014)[60]	Fernandez et al. (2015)[28]

CGI-I = Clinical Global Impression – Improvement; COMT = catechol-O-methyltransferase; CSR = Clinical Study Report; DB = double-blind; EQ-5D-3L = EuroQol 5-Dimensions 3-Level questionnaire; IR = immediate-release; LCIG = levodopa/carbidopa intestinal gel; MOA-B = monoamine oxidase B; MMSE = Mini-Mental State Examination; NR = not reported; OLC = oral levodopa/carbidopa; PD = Parkinson disease; PDHD = Parkinson disease home diary; PDQ-39 = 39-item Parkinson's Disease Questionnaire; PEG- J = percutaneous endoscopic gastrostomy with jejunal extension; QoL = quality of life; RCT = randomized controlled trial; UPDRS = Unified Parkinson's Disease Rating Scale; VAS = visual analogue scale; ZBI = Zarit Burden Interview.

[a] Patient demonstrated identifiable "on" response as established through observation by the investigator. Severe motor fluctuations despite individually optimized treatment were also required.

[b] Optimized therapy was defined as an adequate trial (in the judgment of the investigator) of levodopa/carbidopa, a dopamine agonist, and at least one other class of antiparkinsonian therapy (COMT inhibitor or MAO-B inhibitor).

[c] An adequate trial was defined as failure to achieve therapeutic benefit due to lack of efficacy or intolerability following treatment for a minimum 2 weeks at a minimal dose of at least 33% of the maximally approved dose; or following discontinuation of the study drug due to adverse reactions or intolerability following approved dosing.

[d] Contraindications for PEG-J tube placement included, but were not limited to, the following conditions: pathological changes of the gastric wall, inability to bring the gastric wall and abdominal wall together, blood coagulation disorders, peritonitis, acute pancreatitis, and paralytic ileus.

[e] Collected through PDHD during the 3 days prior to each visit, normalized to a 16-hour waking day. The baseline value was defined as the average normalized "off" time for the 3 PDHD days (after approximately 28 days to stabilize optimal treatment medication) closest to but not on or after the day of the PEG-J procedure.

[f] Two titration periods were conducted using nasojejunal tube and PEG-J tube, each ranging between two days and 14 days.

Source: Study 001/002 CSR,[2] Olanow et al. (2014),[2] Fernandez et al. (2015).[28]

Included Studies

Description of Studies

Double-Blind, Randomized Controlled Trial (Study 001/002)

Studies S187-3-001 and S187-3-002 (N = 36 and N = 35, respectively) were similarly designed DB, double-dummy, multi-centre, multinational, active-controlled, phase III superiority RCTs that recruited patients from centres located in the US, Germany, and New Zealand. Subsequent to discussion with the FDA, the two trials were combined while they were ongoing (due to difficulty with recruitment) — before database lock and any data analyses — to provide one robust RCT, hereafter referred to as Study 001/002 (N = 71).[53]

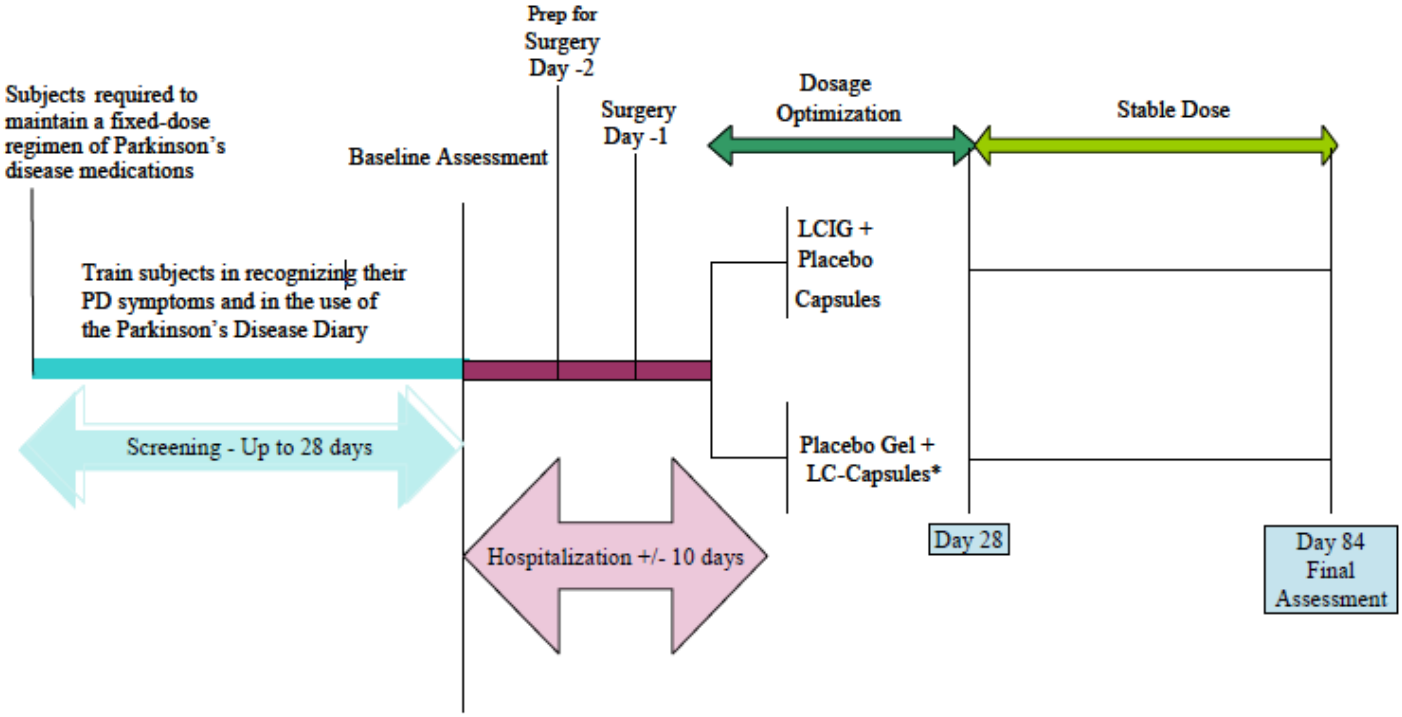
The study objective was to evaluate the efficacy and safety of LCIG for the treatment of patients with advanced levodopa-responsive PD who did not have satisfactory control of severe, debilitating motor fluctuations and hyper-/dyskinesia despite optimized treatment with available combinations of PD medicinal products, and for whom the benefits of this treatment may outweigh the risks associated with the insertion and long-term use of the PEG-J tube required for administration. Further details pertaining to the included study are provided in Table 5.

Study 001/002 consisted of three different phases: a screening phase, a hospitalization phase, and a DB phase. During the screening phase, patients were switched and/or optimally titrated with open-label immediate-release (IR) OLC 100 mg/25 mg. They were also required to achieve a stable dose for other concomitant antiparkinsonian medication, and receive Parkinson disease home diary (PDHD) training. Sustained-released levodopa/carbidopa formulations, levodopa combined with peripheral decarboxylase inhibitors other than carbidopa (e.g., levodopa/benserazide), and apomorphine were to be discontinued. During the hospitalization phase, patients were admitted for up to 10 days as needed for the PEG-J placement. Patients were subsequently randomized (1:1 ratio LCIG: IR OLC and stratified by site) to the DB phase, which consisted of a four-week titration period and an eight-week maintenance period. Details outlining the study design are provided in Figure 2.

Clinic visits were to occur weekly for the first four weeks, then every two weeks through the end of the study. Following the titration period in the DB phase (beyond study week 4), in the weeks when no clinic visit was scheduled, the study site was to contact the patient by telephone. Patients were able to withdraw from participation in this study at any time and for any reason.

Patients who completed Study 001/002 had the option to enrol in an optional 12-month, open-label safety extension study (Study 003). Patients who completed Study 003 were able to enrol in Study 005 for up to five years of follow-up, (Study 003 and Study 005 are summarized in Appendix 6.)

Figure 2: Study 001/002 Design



CSR = Clinical Study Report; LC = levodopa/carbidopa; LCIG = levodopa/carbidopa intestinal gel; PD = Parkinson disease.

Source: Study 001/002 CSR.[26]

Open-Label, Non-Comparative Study (Study 004)

The study design characteristics of the non-comparative multinational, multi-centre, open-label, long-term safety study (Study 004, N = 354) are summarized in Table 5. Patients included in this study were not previously treated with LCIG in Study 001/002. Rescue therapy during the trial was permitted only if clinically indicated. The use of other PD medications was permitted at the investigators' discretion only 28 days post-LCIG initiation. Treatments with either apomorphine or controlled-release OLC formulations were not permitted. Patients who completed Study 004 were able to enrol in Study 005 for up to five years of follow-up (Study 005 is summarized in Appendix 6).

Additional Non-Comparative, Open-Label Studies

A total of 16 prospective, open-label, non-comparative trials were identified in the CDR systematic review. [10-25] The sample size of these trials ranged between nine and 375 enrolled patients and follow-ups ranged between four and 36 months. Treatment with LCIG was administered to all patients. Change from baseline to the last study visits was evaluated for relevant outcomes. Given that Study 004 (also an open-label, non-comparative study) was deemed pivotal by the manufacturer, no further details will be provided in this CDR report for the 16 prospective, open-label, non-comparative trials identified in the systematic review.

Populations

Inclusion and Exclusion Criteria

Double-Blind, Randomized Controlled Trial (Study 001/002)

Investigators were to obtain approval from the Enrolment Steering Committee, which comprised three independent neurologists and movement disorder specialists, prior to enrolling a patient in the study.

Study 001/002 enrolled adults (aged ≥ 30 years) with advanced PD consistent with UK Brain Bank criteria that was complicated by "off" periods that could not be controlled satisfactorily with optimized medical therapy and who were eligible for jejunal placement of a percutaneous gastrojejunostomy tube. Optimized therapy was defined as an adequate trial (in the investigator's judgment) of levodopa/carbidopa, a dopamine agonist, and at least one other class of antiparkinsonian therapy (i.e., a COMT or MAO-B inhibitor). Patients treated with sustained-release levodopa/carbidopa, Stalevo, or other formulations of levodopa were permitted in the study; however, they were switched to equivalent doses of IR OLC 100 mg/25 mg. Patients were to have remained on stable doses for at least four weeks before inclusion. Concurrent antiparkinsonian drugs (apart from apomorphine) were permitted if patients were on stable doses for four weeks before randomization, and if the dose was not changed during the study.

Atypical or secondary parkinsonism, previous neurosurgical treatment for PD, clinically significant medical, psychiatric, or laboratory abnormalities in the judgment of the investigator, or any condition that might interfere with absorption, distribution, metabolism, or excretion of study drug or contraindicate placement of a PEG-J tube were all considered criteria for exclusion.

Open-Label, Non-Comparative Study (Study 004)

Patients ≥ 30 years of age who were levodopa-responsive meeting the UK Parkinson's Disease Society Brain Bank diagnostic criteria and who had severe motor fluctuations, defined as ≥ 3 hours of daily "off" time at baseline (confirmed through PD diary) despite currently available optimized PD therapies, were included in Study 004.

Baseline Characteristics

Double-Blind, Randomized Controlled Trial (Study 001/002)

Details of patients' baseline characteristics are presented in Table 6, Table 7, and Table 8. Generally, the distributions of baseline patient characteristics were well balanced across treatment groups.

Patients enrolled in Study 001/002 had a mean age of 64.4 years (standard deviation [SD]: 8.3); approximately half (51%) were under 65 years of age. Overall, more patients over 65 years of age were randomized to the PBO LCIG + IR OLC capsules group compared with the LCIG + PBO IR OLC capsules group (56% compared with 43%, respectively). Most enrolled patients were male (65%), non-Hispanic or Latino (96%), or white (93%), and were located in the US (73%).

The mean PD duration was 10.9 years (SD 5.2). Patients in the LCIG + PBO IR OLC group had a shorter duration of PD in comparison with patients in the PBO LCIG + IR OLC

capsules group (10.0 years versus 11.8 years). All patients (100%) had symptoms of bradykinesia and muscular rigidity; most had tremor (78%) and postural instability (65%).

Patients in the LCIG + PBO IR OLC capsules group had lower mean “off” time compared with the PBO LCIG + IR OLC capsules group (6.3 hours versus 7.0 hours, respectively), and had a greater mean “on” time without troublesome dyskinesia (8.7 hours versus 7.8 hours respectively).

Mini-Mental State Examination (MMSE), Clinical Global Impression – Improvement (CGI-I), and UPDRS scores were similar between groups, with the exception of the UPDRS Part III (18.1 compared with 22.5) and Part I, II, and III overall scores (31.5 compared with 35.8 in the LCIG + PBO IR OLC capsules and the PBO LCIG + IR OLC capsules groups, respectively) and the PDQ-39 summary index score (35.1 compared with 38.6 in the LCIG + PBO IR OLC capsules and PBO LCIG + IR OLC capsules groups, respectively).

Approximately half (54%) of all the randomized patients were treated with three or more PD medications at baseline. Most patients (68%) were treated with dopamine agonists, with more patients in the PBO LCIG + IR OLC capsules group (76%) receiving dopamine agonists compared with the LCIG + PBO IR OLC capsules group (59%). Approximately half (46%) of all patients were treated with COMT inhibitors, with fewer patients in the PBO LCIG + IR OLC capsules group (44%) receiving COMT inhibitors compared with the LCIG + PBO IR OLC capsules group (49%). The minority of patients (30%) were treated with MAO-B inhibitors, with fewer patients in the PBO LCIG + IR OLC capsules group (18%) receiving MAO-B inhibitors compared with the LCIG + PBO IR OLC capsules group (41%).

Overall, patients in both groups were treated with a mean daily levodopa dose of 1,062.0 mg (SD 427.7). Patients in the PBO LCIG
+ IR OLC capsules group were treated with greater daily doses of levodopa compared with the LCIG + PBO IR OLC capsules group (1,005.4 mg versus 1,123.5 mg).

The majority of patients in both groups were historically treated with dopamine agonists (90%), MAO-B inhibitors (61%), or other dopaminergic drugs (72%), whereas approximately half (44%) were treated with adamantane derivatives. All patients (100%) were historically treated with dopamine or dopamine derivatives.

Open-Label, Non-Comparative Study (Study 004)

The baseline characteristics reported in Study 004 are summarized in Table 6, Table 7, and Table 8. Patients had a mean age of 64.1 (SD: 9.1). The majority of the patients were male (57%); 93% were white. Patients had lived an average of 12.5 (5.5) years with PD and were receiving a mean of 1,082.9 mg of levodopa per day (582.1). The majority of the patients (59%) were treated with two or more PD medications at baseline, of which the majority were levodopa or levodopa derivatives (73%) and dopamine agonists (55%). The mean hours per day of “off” time, “on” time without troublesome dyskinesia, and “on” time with troublesome dyskinesia were 6.75 (2.35), 7.65 (2.45), and 1.61 (2.03), respectively. The mean UPDRS overall score (Part I, II, and III) for patients was 48.4 (18.9); the mean Clinical Global Impression – Severity (CGI-S) score was 4.85 (0.85); the mean PDQ-39 score was 42.8 (15.1); the mean EuroQol 5-Dimensions (EQ-5D) summary index score was 0.588 (0.195); and the mean EuroQuol visual analogue scale (EQ VAS) score was 50.2 (21.0).

The minority (28%) of patients were not receiving any additional PD medications during Study 004, whereas, approximately half (52%) were taking one PD medication. The

majority (68%) of patients were treated with levodopa or derivatives and approximately half (49%) were treated with levodopa only.

Table 6: Summary of Baseline Demographic Characteristics

Characteristics	Study 001/002 (Safety Set)		Study 004
	LCIG + PBO IR OLC Capsules N = 37	PBO LCIG + IR OLC Capsules N = 34	LCIG N = 354
Age			
Mean years (SD)	63.7 (9.5)	65.1 (6.8)	64.1 (9.1)
Median (min, max)	64.0 (39.0, 83.0)	66.0 (45.0, 79.0)	NR
Age Category, n (%)			
< 65 years	21 (57)	15 (44)	NR
≥ 65 years	16 (43)	19 (56)	NR
Gender, n (%)			
Male	24 (65)	22 (65)	202 (57)
Female	13 (35)	12 (35)	152 (43)
Ethnicity, n (%)			
Hispanic or Latino	2 (5)	1 (3)	NR
Non-Hispanic or Latino	35 (95)	33 (97)	NR
Race, n (%)			
American Indian or Alaska Native	1 (3)	0	NR
Asian	1 (3)	3 (9)	22 (6)
White	35 (95)	31 (91)	328 (93)
Black	NR	NR	4 (1)
Country, n (%)			
Germany	7 (19)	9 (27)	NR
New Zealand	1 (3)	2 (6)	NR
US	29 (78)	23 (68)	NR

IR = immediate-release; LCIG = levodopa/carbidopa intestinal gel; max = maximum; min = minimum; NR = not reported; OLC = oral levodopa/carbidopa; PBO = placebo; SD = standard deviation.

Source: Study 001/002 Clinical Study Report,[26] Fernandez et al. (2015).[28]

Table 7: Summary of Baseline Parkinson Disease Characteristics

Characteristics	Study 001/002 (Safety Set)		Study 004
	LCIG + PBO IR OLC Capsules N = 37	PBO LCIG + IR OLC Capsules N = 34	LCIG N = 354
Duration of PD			
Mean years, (SD)	10.0 (4.6)	11.8 (5.6)	12.5 (5.5)
Median, (min, max)	9.4 (1.7, 22.1)	10.8 (4.3, 30.8)	NR
Diagnosis of bradykinesia, n (%)	37 (100)	34 (100)	NR
Diagnosis of muscular rigidity, n (%)	37 (100)	34 (100)	NR
Diagnosis of 4 Hz to 6 Hz resting tremor, n (%)	28 (76)	27 (79)	NR
Diagnosis of postural instability, n (%)	23 (62)	23 (68)	NR
Mean "On" or "Off" Time, Hours per Day (SD)[a]			
"Off" time	6.3 (1.7)	7.0 (2.1)	6.75 (2.35)
"On" time without troublesome dyskinesia[b]	8.7 (2.0)	7.8 (2.5)	7.65 (2.45)
"On" time without dyskinesia	6.3 (2.7)	5.6 (3.2)	NR
"On" time with non-troublesome dyskinesia	2.4 (1.8)	2.2 (2.2)	NR
"On" time with troublesome dyskinesia	1.0 (1.6)	1.2 (1.7)	1.61 (2.03)
Mean MMSE total score, (SD)	28.7 (1.4)	28.9 (1.4)	NR
Mean UPDRS Score (SD)[a]			
Part I	1.8 (1.7)	1.8 (1.8)	NR
Part II	11.6 (6.9)	11.8 (7.0)	17.4 (6.6)
Part III	18.1 (9.9)	22.5 (11.7)	28.8 (13.7)
Overall (Part I, II, and III)	31.5 (15.6)	35.8 (18.9)	48.4 (18.9)
Part IV score (dyskinesia-related items)	2.4 (1.6)	2.5 (2.0)	3.7 (2.4)
Part IV score (total)	7.9 (2.2)	7.9 (3.0)	NR
PDQ-39 summary index score (SD)[a]	35.1 (18.0)	38.6 (17.9)	42.8 (15.1)
CGI-S score (SD)[a]	4.2 (0.7)	4.6 (0.8)	4.85 (0.84)
EQ-5D-3L summary index score	0.692 (0.151)	0.617 (0.181)	0.588 (0.195)
EQ VAS	63.9 (14.6)	57.0 (18.8)	50.2 (21.0)

CGI-S = Clinical Global Impression – Severity; CSR = Clinical Study Report; EQ-5D-3L = EuroQol 5-Dimensions 3-Levels questionnaire; EQ VAS = EuroQol 5-Dimensions visual analogue scale; IR = immediate-release; LCIG = levodopa/carbidopa intestinal gel; max = maximum; min = minimum; MMSE = Mini-Mental State Examination; NR = not reported; OLC = oral levodopa/carbidopa; PBO = placebo; PD = Parkinson disease; PDQ-39 = 39-item Parkinson's Disease Questionnaire; SD = standard deviation; UPDRS = Unified Parkinson's Disease Rating Scale.

[a] Based on the full analysis set, which included 36 patients in the intestinal gel group and 33 patients in the IR group.

[b] "On" time without troublesome dyskinesia equals "on" time without dyskinesia plus "on" time with non-troublesome dyskinesia.

Source: Study 001/002 CSR,[2], Fernandez et al. (2015).[28]

Table 8: Summary of PD Medications at Baseline

Characteristics	Study 001/002 (Safety Set)		Study 004
	LCIG + PBO IR OLC Capsules N = 37	PBO LCIG + IR OLC Capsules N = 34	LCIG N = 354
Number of PD Medications, n (%)			
1	6 (16)	2 (6)	94 (27)
2	12 (32)	13 (38)	112 (32)
3	8 (22)	11 (32)	87 (25)
> 3	11 (30)	8 (24)	60 (17)
Daily Levodopa Dose			
Mean dose, mg (SD)	1,005.4 (373.6)	1,123.5 (477.9)	1,082.9 (582.1)
Median dose, mg (min, max)	950.0 (500, 2200)	1,150.0 (400, 2200)	NR
Antiparkinsonian Medication, n (%)			
Levodopa or derivatives	37 (100)	34 (100)	259 (73)
Dopamine agonist	22 (59)	26 (76)	196 (55)
COMT inhibitor	18 (49)	15 (44)	100 (28)
Amantadine	5 (14)	11 (32)	106 (30)
MAO-B inhibitor	15 (41)	6 (18)	45 (13)
Tertiary amines	0	2 (6)	11 (3)
Historical Response, n (%)			
Adamantane Derivatives	12 (32)	19 (56)	NR
Effective	4 (33)	8 (42)	NR
Partially effective	6 (50)	7 (37)	NR
Not effective	2 (17)	1 (5)	NR
Dopamine and Dopamine Derivatives	37 (100)	34 (100)	NR
Effective	23 (62)	24 (71)	NR
Partially effective	14 (38)	10 (29)	NR
Not effective	0	0	NR
Dopamine Agonists	32 (87)	32 (94)	NR
Effective	16 (50)	19 (59)	NR
Partially effective	13 (41)	8 (25)	NR
Not effective	3 (9)	3 (9)	NR
MAO-B Inhibitors	22 (60)	21 (62)	NR
Effective	4 (18)	10 (48)	NR
Partially effective	13 (59)	4 (19)	NR
Not effective	3 (14)	6 (29)	NR
Other Dopaminergic Agents	25 (68)	26 (77)	NR
Effective	12 (48)	14 (54)	NR
Partially effective	8 (32)	7 (27)	NR
Not effective	4 (16)	2 (8)	NR

COMT = catechol-O-methyltransferase; CSR = Clinical Study Report; IR = immediate-release; LCIG = levodopa/carbidopa intestinal gel; max = maximum; min = minimum; MAO-B = monoamine oxidase B; NR = not reported; OLC = oral levodopa/carbidopa; PBO = placebo; PD = Parkinson disease; SD = standard deviation.

Source: Study 001/002 CSR,[26] Fernandez et al. (2015).[28]

Interventions

Double-Blind, Randomized Controlled Trial (Study 001/002)

Overall, patients were asked to refrain from making any significant dietary changes during the study given that high protein diets could affect the efficacy of treatment with levodopa/carbidopa.

Screening Phase

During the screening phase (up to 28 days), patients treated with formulations other than IR OLC 100 mg/25 mg were switched to the latter. Doses of open-label IR OLC 100 mg/25 mg were subsequently titrated to optimize response and minimize AEs. If a fixed-dose regimen could not be achieved during this phase, randomization to the DB treatment phase was to be delayed until a stable regimen could be maintained for a full 28-day period. The conversion did not require a stabilization period if prior combination therapies contained a 4:1 formulation of levodopa/carbidopa 100 mg/25 mg IR (e.g., Stalevo 100). Patients were also required to achieve a stable dose for other concomitant antiparkinsonian medications unless contraindicated.

Most PD treatments were permitted with the exception of sustained-released levodopa/carbidopa formulations, levodopa combined with peripheral decarboxylase inhibitors other than carbidopa (e.g., levodopa/benserazide), and apomorphine.

Hospitalization Phase

Following the screening phase, patients were to be admitted to hospital for approximately 10 days, as needed, two days prior to PEG-J placement for pre-surgical procedures. The PEG-J tube was implanted on the day after admission by a qualified gastroenterologist or surgeon experienced with the placement and maintenance of PEG-J tubes and possessing a thorough knowledge of endoscopy, aspects of PD and neurological patients, and the LCIG infusion system and its related procedures.

A single dose of prophylactic antibiotics, such as first- or third-generation cephalosporin (or those with similar coverage) were required to be administered approximately 30 minutes prior to the PEG-J procedure.

Double-Blind Phase

Randomization was conducted centrally using an interactive voice response system (IVRS). It was based on computer-generated, predetermined, randomization codes and stratified by site, with a mixed block size of two or four. Patients who were implanted with a PEG-J tube were randomized in a 1:1 ratio (LCIG:IR OLC). Study 001/002 was a double-dummy design; therefore, patients received either LCIG for infusion in addition to over-encapsulated oral placebo or IR OLC 100 mg/25 mg in addition to placebo intestinal gel for infusion.

LCIG was delivered as an aqueous solution containing 20 mg/mL levodopa and 5 mg/mL carbidopa monohydrate packaged in
100 mL cassettes or matching placebo gel containing sodium carboxymethylcellulose solution alone, administered as a morning bolus dose (5 mL to10 mL) followed by continuous infusion at a constant rate for the remainder of each patient's waking day (approximately 16 hours). Infusions were stopped overnight. The tubing was to be disconnected from the pump and flushed with potable water every night.

IR OLC capsules 100 mg/25 mg or matching placebo capsules were administered at the same dose and frequency as determined during the screening phase (baseline dose and frequency) throughout the waking day (approximately 16 hours) and began at the same time as the infusion. The smallest possible dose of the IR OLC or matched placebo was one single capsule (the only available formulation).

Typical routine night-time treatment with open-label IR OLC 100 mg/25 mg capsules was permitted. Night-time doses (between daily discontinuation of study drug and up to two hours prior to the administration of the morning dose) were not considered as rescue medication; however, they were to be recorded in the daily dosing diary.

All patients, caregivers, and investigators were blinded to treatment allocation. Data analysts were also masked until after the database was locked. Furthermore, to maintain the integrity of the DB, double-dummy nature of the study, patients were not allowed to split or divide levodopa/carbidopa or matching placebo capsules. Furthermore, the last scheduled daily oral capsule dose was required to be a single capsule (levodopa/carbidopa 100 mg/25 mg IR or matching placebo), which allowed for the required end-of-infusion PEG-J flush (3 mL of LCIG gel infusion in the dead space of the tubing, equal to approximately 60 mg of levodopa). Any change in the dose of an active intervention in a participant had to be matched by a corresponding change in the alternative treatment, so that both treatments (active and placebo) for each patient were adjusted at the same time. In this way, the masking was maintained for patients in both groups to maintain the integrity of the masking. Masking of participants and investigators was not formally assessed.

Titration Period

Study 001/002 had a second titration period during the DB phase in which the LCIG and IR OLC doses along with their matching placebo doses were optimally titrated for four weeks. Dosing could be adjusted once daily during the first two weeks (during an in-patient hospital stay) and weekly thereafter (during scheduled outpatient visits).

During this second titration period, the morning bolus dose of LCIG (or matching placebo gel) was initially administered at 80% of the usual optimally titrated oral levodopa morning dose established prior to randomization (screening phase).

The initial continuous infusion dose (i.e., the continuous infusion rate over the 16-hour waking day) was calculated based on the total oral daily dose minus the morning dose and the last dose of the day. The initial continuous daily dose was divided by 16 hours to determine the continuous hourly dose. Only the doses of IR OLC 100 mg/25 mg tablets taken during the waking 16-hour day were used to calculate the total oral daily dose (i.e., they did not include the doses of levodopa/carbidopa that were taken at night when the continuous infusion was not administered).

Continuous infusion of LCIG or matching placebo gel could be adjusted by changing the levodopa infusion rate in 100 mg daily increments based on the investigator’s judgment of efficacy of the previous day's dose and any oral rescue doses (patients were not permitted to make any adjustments).

Given that simultaneous titration of active and placebo therapies was required for patients in both groups, IR OLC could be adjusted by increasing one or more doses by 100 mg; however, the frequency of dosing could not be changed.

If judged absolutely necessary by the investigator, temporary disruption of both the gel and capsule formulations was permitted for patients who developed unsafe dyskinesia or other levodopa-related complications until symptoms had improved to a clinically acceptable level. If treatment was interrupted, patients were required to stop both active and placebo treatments in order to maintain the DB, double-dummy study design. Patients were subsequently treated with open-label IR OLC 100 mg/25 mg capsules (as per the dose received prior to randomization and adjusted as clinically indicated) until the problem was resolved and the gel infusion could be resumed. If cessation of treatment lasted less than 24 hours, treatment was resumed the following morning at the same dose (infusion gel and oral) received prior to the interruption. If cessation lasted longer than 24 hours, the investigator was to consult the medical monitor prior to restarting treatment.

Maintenance Period

The titration phase was followed by a maintenance phase (eight weeks) during which patients were maintained on stable doses of their assigned treatments. Adjustments beyond the titration period (study week 4) were not permitted. However, an exception was made when a decrease in the study drug was clinically indicated in order to manage AEs. Open-label IR OLC could be used as rescue therapy for persistent “off” episodes for patients in either group.

Open-Label, Non-Comparative Study (Study 004)

LCIG was delivered as an aqueous solution containing 20 mg/mL levodopa and 5 mg/mL carbidopa monohydrate packaged in

100 mL cassettes administered as morning bolus doses followed by continuous infusion at a constant rate for the remainder of each patient’s waking day (approximately 16 hours) with additional rescue doses during the day, if clinically indicated. Infusions were stopped overnight and typical routine night-time treatment with IR OLC was permitted. The initial infusion doses of LCIG were based on patients’ previous dose of daily OLC. During the screening period (up to 28 days), patients received PD diary training and were converted to and stabilized on levodopa monotherapy. All patients were subsequently hospitalized for the placement of the NJ and PEG-J tubes and initiation of LCIG titration. Study 004 consisted of two titration periods. The first (up to 14 days) was a test period for LCIG infusion through an NJ tube followed by a dose-optimizing titration period (up to 14 days) through a PEG-J tube. Once patients were optimally titrated, they entered the long-term PEG-J treatment period (up to 54 weeks). Assessments began on day 28 of the period.

Outcomes

Double-Blind, Randomized Controlled Trial (Study 001/002)

During the screening phase, patients (and caregivers, if applicable) were instructed on how to understand PD symptoms and how to complete the PDHD through an instruction DVD. Patients were required to have at least 75% concordance with investigator rating and at least 75% compliance in completion of the PDHD to meet the inclusion criteria of the study.

The evaluation of compliance could not be repeated due to inadequate “off” time (less than three hours per day on each of the three days). If no transitions occurred between “off” and “on” states during the time of concordance evaluation or if concordance and compliance were lower than 75%, the time (screening period) in which concordance was evaluated

could be prolonged. For patients who did not achieve the compliance criteria (75%), retraining in completion of the PDHD was required prior to re-evaluation of compliance with the diary.

Study visits were done at baseline, weekly through study week 4 (weeks 1, 2, 3, and 4), and biweekly thereafter (weeks 6, 8, 10, and 12). The PDHD was to be completed by patients every 30 minutes for 24 hours for three consecutive days prior to each visit and should have indicated if they were in an "off" state, "on" state without dyskinesia, "on" state with non-troublesome dyskinesia, "on" state with troublesome dyskinesia, or "asleep." If patients were unable to complete their diaries, their caregivers were to complete the entries on their behalf. During the assessment days, no rescue doses of IR OLC were to be taken because of their potential impact on efficacy measures, unless absolutely required (medically necessary). One study conducted by Hauser et al. suggests that a one-hour reduction in "off" time was considered to be a minimal clinically important difference (MCID) in actively treated patients.[61] More information regarding the PDHD can be found in Appendix 5.

Primary Outcome

The primary efficacy outcome was change between baseline and final visit (week 12) in the mean number of "off" hours collected on the PDHD during the three consecutive days prior to study visit, normalized to a 16-hour waking day. Normalized "off" time was calculated by dividing the absolute "off" time by the daily awake time (defined as the sum of absolute "off" time, "on" time without dyskinesia, "on" time with non-troublesome dyskinesia, and "on" time with troublesome dyskinesia) and multiplying by 16 hours. The baseline value was defined as the average normalized "off" time for the three PDHD days closest to, but not on or after, the day of the PEG-J procedure. If only two valid symptom diary days were available prior to a clinic visit, data from the two days were used to calculate the average daily "off" time. If only one valid symptom diary day was available, the average daily from the previous week was be averaged with the daily "off" time from the one valid diary day. Patients with no valid symptom diary days for a visit or who were completely missing a visit had the average daily "off" time set to missing for that visit.

Key Secondary Outcome

The predefined key secondary outcome was change from baseline to final visit (week 12) in the mean number of normalized "on" hours without troublesome dyskinesia (defined as a composite of "on" time without dyskinesia and "on" time with non-troublesome dyskinesia) collected in the PDHD during the three consecutive days prior to the study visit. The baseline value was defined as the average normalized "on" time for the three PDHD days closest to but not on or after the day of the PEG-J procedure.

Secondary Outcomes

Other secondary outcome measures included change from baseline in PDQ-39 summary index score, CGI-I score, UPDRS Part II (ADL subscore), UPDRS Part III (motor subscore), EuroQol 5-Dimensions 3-Levels questionnaire (EQ-5D-3L) summary index score, and Zarit Burden Interview (ZBI) score. More information regarding the secondary outcomes can be found in Appendix 5.

Parkinson's Disease Questionnaire 39

The PDQ-39 is a self-administered, disease-specific instrument of HRQoL (HRQoL) designed to measure aspects of health not captured under general health questionnaires

that may be relevant to patients with PD. The PDQ-39 comprises 39 items addressing eight domains considered to be adversely affected by the disease, including:

- Mobility (e.g., fear of falling when walking)
- ADL (e.g., difficulty cutting food)
- Emotional well-being (e.g., feelings of isolation)
- Stigma (e.g., social embarrassment)
- Social support
- Cognition
- Communication
- Bodily discomfort

The PDQ-39 scores ranged between 0 and 100, with lower scores indicating a better-perceived health status. Findings from one study conducted by Peto et al. showed a varying mean MCID for different domains: mobility (–3.2), ADL (–4.4, emotional well-being (–4.2), stigma (–5.6), social support (–1.4), cognitions (–1.8), communications (–4.2), bodily discomfort
(–2.1), and summary index score (–1.6).[62]

Clinical Global Impression – Improvement

The CGI-I scale is a global assessment of the change in a patient's clinical status. Baseline scores were established through the CGI-S two days prior to randomization. Scores on the Severity of Illness subscale range from 1 ("not ill at all") to 7 ("among the most extremely ill"). The CGI-I is rated from 1 to 7 where 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse. No MCID was identified in PD.

Unified Parkinson's Disease Rating Scale

The UPDRS is a standard investigator rating tool for measuring parkinsonian signs and symptoms. The UPDRS assessments were administered by qualified individuals (third-party trained and certified raters). Every effort was made to ensure that each patient was rated by the same rater throughout the study.

The UPDRS comprises the following sections:

- Part I – Mentation, Behaviour, and Mood (4 items; possible scores range between 0 and 16)
- Part II – Activities of Daily Living (13 items; possible scores range between 0 and 52)
- Part III – Motor Examination (14 items; possible scores range between 0 and 56)
- Part IV – Complications of Therapy (including dyskinesias; [11 items; possible scores range between 0 and 23])

The UPDRS assessments were performed at the same time of day throughout the study during "off" times (only during the screening phase) defined as the morning prior to the patients taking their first daily dose of antiparkinsonian medication and during the best "on" time (throughout the study), defined as two to four hours following the morning dose of study drug or PD medications, but prior to lunch. Individual items in parts I to III are scored on a 5-point scale (0 to 4), with higher scores indicating worse symptoms, while Part IV also includes a number of items for which scoring is 0 (no) or 1 (yes). A total UPDRS (Part I to

IV) score of 0 represents “no disability” and a score of 199 represents “worst disability.” Among available studies, the estimated MCID for the ADL component (Part II) and motor component (Part III) were 2.3 and 6.5 points, respectively, in patients with advanced PD.[63]

EuroQol 5-Dimensions 3-Levels

The EQ-5D-3L is a generic HRQoL instrument that may be applied to a wide range of health conditions and treatments. The first of two parts of the EQ-5D-3L is a descriptive system that classifies respondents (aged ≥ 12 years) based on the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D-3L has three possible levels
(1, 2, or 3) for each domain, representing “no problems,” “some problems,” and “extreme problems,” respectively. Index scores less than 0 represent health states that are valued by society as being worse than dead, while scores of 0 and 1.00 are assigned to the health states “dead” and “perfect health,” respectively. The second part is a 20 cm visual analogue scale (the EQ VAS) that has end points labelled 0 and 100, with respective anchors of “worst imaginable health state” and “best imaginable health state.” Although the MCID for the EQ-5D-3L in PD remains unclear, differences of 0.033 to 0.074 in the index score are typically clinically meaningful in other conditions. A systematic review reported an estimated MCID of 0.10 (range: 0.04 to 0.17) and 0.11 (range: 0.08 to 0.14) based on the UPDRS and PSQ-39 score, respectively; however, these PD-specific MCIDs were obtained from a conference abstract, and, as such, limited information was presented on the methodology used in their estimation.[64]

Zarit Burden Interview

The ZBI is a self-administered 22-item questionnaire measuring caregiver burden. The questions refer to the caregiver/patient relationship and evaluate the caregiver's health condition, psychological well-being, finances, and social life. The caregiver burden
is evaluated by the total score obtained from the sub-total of 22 questions. The ZBI was not completed if the patient did not have a caregiver. Each of the 22 items are scored on a 5-point Likert scale, ranging from 0 (never) to 4 (nearly always). Scores are then summed to create a total score that can range between 0 and 88, with higher score indicating greater burden. No MCID was identified in PD.

Other Outcomes

Other “on” time outcomes included the change from baseline to final visit (week 12) in the mean number of “on” hours without dyskinesia, with non-troublesome dyskinesia, and with troublesome dyskinesia recorded in the PDHD during the three consecutive days prior to study visit. The baseline value was defined as the average normalized “on” time for the three PDHD days closest to but not on or after the day of the PEG-J procedure.

Harms

An independent Data Safety Monitoring Board (DSMB) composed of three members (including two physicians whose expertise included neurology or gastroenterology and a biostatistician with clinical experience) reviewed unblinded safety data and provided the sponsor with recommendations regarding study modification, continuation, or termination. A dedicated charter in accordance with the FDA Guidance for Clinical Trial Sponsors/Establishment and Operation of Clinical Trial Data Monitoring Committees (March 2006) and the European Medicines Agency/Committee for Medicinal Products for Human Use Guideline on Data Monitoring (January 2006) was developed to address the mode of operations of the DSMB so that the integrity of the study was protected.

AEs were defined as any untoward medical occurrences in a patient-administered medicinal product (or a system consisting of drug, device, and surgical procedure) and which does not necessarily have a causal relationship with this treatment. Therefore, an AE can be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom (including an AE occurring from drug abuse, drug withdrawal, or any failure of expected pharmacological action), or disease temporally associated with the use of a medicinal product or device, whether or not considered related to the medicinal product or device.

SAEs were defined as any untoward medical occurrence that at any dose that resulted in death or was life-threatening (an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if the event were more severe); required in-patient hospitalization or prolongation of an existing hospitalization; resulted in persistent or significant disability/incapacity; or was considered a congenital anomaly/birth defect.

Open-Label, Non-Comparative Study (Study 004)

The primary objective was to evaluate the long-term safety of LCIG based on AEs, device complications, and number of completers. All AEs were considered as treatment-emergent adverse events (TEAEs), defined as those that began or worsened from the time of NJ tube insertion until 30 days after PEG-J removal.

Long-term efficacy (as measured by "off" time, "on" time with and without troublesome dyskinesia, UPDRS) and QoL (as measured by PDQ-39, EQ-5D-3L, EQ VAS, and CGI-I) were evaluated as secondary end points.

Statistical Analysis

Double-Blind, Randomized Controlled Trial (Study 001/002)

Determination of Sample Size

Study 001/002 was designed as a superiority trial to assess the beneficial effects of LCIG using the change from baseline in normalized "off" time as the primary end point. Based on available literature (including trials with similar study design and other compounds used for the management of advanced-stage PD using the change from baseline in "off" time as a primary efficacy end point), a difference of 2.5 hours between LCIG and IR OLC in change in "off" time hours from baseline and an SD of 2.85 were assumed to be reasonable.[51,65,66] Further, no more than 5% of the randomized patients were expected to be excluded from the full analysis set (FAS). Based on these assumptions, a sample size of approximately 62 patients (31 patients using a 1:1 randomization ratio) would give 90% power to detect a difference between the LCIG and IR OLC groups at the alpha = 0.05 level of significance.

Primary End Point

The primary analysis of the primary end point (change in normalized "off" time) was conducted in the FAS population using an analysis of covariance (ANCOVA) model stratified by treatment group and country as fixed effects and with baseline "off" time, and natural logarithm of mean daily dose of rescue levodopa on days with non-missing PDHD data as covariates. Missing data were imputed based on the last observation carried forward (LOCF) approach. Patients with more than one observation for the same 30-minute time period split the time evenly among the number of events (e.g., recorded as 15 minutes "on" and 15 minutes "off"). Patients who did not complete at least 12 awake hours of PDHD

data (excluding time asleep) had that daily data set to missing (i.e., the data set was not considered as a valid PDHD day) and there was no imputation of data for these days. The average daily dose of rescue levodopa on non-missing PDHD days was calculated as the total milligrams of levodopa taken as a rescue dose on valid PDHD days divided by the number of non-missing PDHD days in the DB phase. Data were presented as least squares mean difference (LSMD) in the change from baseline compared with IR OLC, with corresponding 95% confidence intervals (CI). Treatment with LCIG was to be considered superior to IR OLC if the two-sided *P* value was less than or equal to 0.05.

Sensitivity Analyses

Sensitivity analyses were also performed for the primary end point and analyzed using a mixed-effects models for repeated measures (MMRM) model using an unstructured matrix for the covariance of the within-participant repeated measures, which included change from baseline as a fixed effect covariate and treatment, country, and time (scheduled assessment visits) as fixed effect (categorical) factors. The MMRM also considered time by treatment interaction as well as time by baseline interaction.

Further sensitivity analyses were also performed for the primary end point at the request of the FDA, and were conducted in a manner similar to those used for the primary analysis (i.e., ANCOVA). However, the sensitivity analyses considered different approaches to the primary ANCOVA analysis by excluding the covariate of rescue medication on valid PDHD days, including the covariate of rescue medication over the treatment period, including the values on final PDHD days with rescue medication use replaced by average daily normalized “off” time at baseline, and excluding values on final PDHD days with rescue medication use.

All sensitivity analyses were not adjusted for multiple statistical tests.

Subgroup Analyses

The treatment effect on the primary efficacy end point was also evaluated within each of the following pre-specified subgroups: gender, race, age (< 65 or ≥ 65 years), country (US, ex-US), and duration of PD (< 10 or ≥ 10 years). Only the duration-of-PD subgroup was of interest for this review (identified in Table 4). Subgroup analyses were not to be completed for subgroups comprising < 20% of the randomized patients. No hypothesis testing was to be performed on these subgroups for this study.

Subgroup analyses were also performed in the FAS population and were analyzed in a manner similar to the primary end point (i.e., ANCOVA). Randomization was not stratified for any of the pre-specified subgroups and none of the subgroup analyses were adjusted for multiple statistical tests.

Secondary End Points

All secondary end point analyses were performed in the FAS population and analyzed in a manner similar to the primary end point (i.e., ANCOVA), and included effects for treatment, country, and corresponding baseline variables as a covariate. Missing data for secondary end points was also imputed using the LOCF method.

Pre-specified hierarchical testing and a gatekeeping procedure were used to maintain the family-wise error rate at 0.05. This method allows testing at a significance level of 0.05 without adjustment. Subsequent to the statistical significance (at alpha = 0.05) of the primary efficacy variable, a testing hierarchy was performed on the secondary efficacy

variables. The statistical testing hierarchy stopped when an end point was found to be statistically insignificant at alpha = 0.05.

The statistical testing order was as follows:

- "On" time without troublesome dyskinesia (“on” time without dyskinesia or with non-troublesome dyskinesia) at week 12
- PDQ-39 summary index score at week 12
- CGI-I score at week 12
- UPDRS Part II score at week 12
- UPDRS Part III score at week 12
- EQ-5D-3L summary index score at week 12
- ZBI score at week 12

Harms

Proportions of patients with at least one AE, SAE, and AE leading to discontinuation were summarized and compared between treatment groups using descriptive statistics. For safety end points, all analyses were based on the observed data (i.e., with no imputation of missing data) and the safety set.

Open-Label, Non-Comparative Study (Study 004)

A sample of 320 patients was planned to satisfy regulatory requirements for exposure assessments at six and 12 months.

All efficacy outcomes were based on the mean within-group change from baseline to the last study visit. A one-sample t-test was used to assess within-group changes from baseline to each visit and end point. No adjustments for multiple statistical testing were performed.

Analysis Populations

Double-Blind, Randomized Controlled Trial (Study 001/002)

Efficacy was assessed in the FAS, which included all randomly allocated participants with data for baseline and at least one post-baseline assessment. The completers set was a pre-specified subset of the FAS that included only patients who completed the study.

Safety was assessed in the safety set, which included all randomly allocated patients (all patients who underwent the PEG-J procedure).

Open-Label, Non-Comparative Study (Study 004)

All patients who received LCIG during the post-PEG-J period and who completed at least one post-baseline assessment were included in the efficacy analyses, whereas all patients who had NJ placement and completed at least one post-baseline safety assessment were included in all safety analyses.

Patient Disposition

Double-Blind, Randomized Controlled Trial (Study 001/002)

Of the 97 patients screened in Study 001/002, approximately 27% did not meet the criteria for enrolment. The most common reason for exclusion was protocol violations (78%) followed by withdrawal of consent (20%) and AEs (4%). The majority of patients completed the study through week 12 (93%). A similar number of patients discontinued the study across treatment groups (5% compared with 9% in the LCIG + PBO IR OLC capsules and PBO LCIG + IR OLC capsules groups, respectively). The most common reason for discontinuation in both groups was AEs.

A similar number of patients deviated from the protocol across treatment groups (24% compared with 27% in the LCIG + PBO IR OLC capsules and PBO LCIG + IR OLC capsules groups, respectively). The most common reason for protocol deviations was receiving the wrong treatment or an incorrect dose (22% compared with 27% in the LCIG + PBO IR OLC capsules and PBO LCIG + IR OLC capsules groups, respectively). Details about patient disposition in Study 001/002 are provided in Table 9.

Open-Label, Non-Comparative Study (Study 004)

The patient disposition is summarized in Table 9. Of the 422 patients screened in Study 004, approximately 16% did not meet the criteria for enrolment. The majority of patients completed the study through the NJ tube test period (92%). The most common reasons for discontinuation were AEs (8%) and withdrawal of consent (8%). The majority of patients completed Study 004 through the PEG-J treatment phase (77%).

Table 9: Patient Disposition

Disposition	Study 001/002 (Safety Set)		Study 004
	LCIG + PBO IR OLC Capsules	PBO LCIG + IR OLC Capsules	ALL LCIG
Screened, N	97		422
Randomized, N (%)	71 (73)		354[a]
Randomized, N	37	34	
Completed the study, n (%)	35 (95)	31 (91)	272 (77)
Discontinued the Study, n (%)	2 (5)	3 (9)	82 (23)
Adverse event	1 (3)	2 (6)	27 (8)
Administrative	NR	NR	14 (4)
Withdrew consent	NR	NR	25 (8)
Lack of efficacy	0	1 (3)	7 (2)
Protocol violation	1 (3)	0	9 (3)
Protocol Deviations, n (%)	9 (24)	9 (27)	NR
Patient did not meet entry criteria, n (%)	1 (3)	0	NR
Patient received the wrong treatment or incorrect dose, n (%)	8 (22)	9 (27)	NR
Patient received excluded concomitant treatment, n (%)	1 (3)	1 (3)	NR
Full Analysis Set, N (%)	36 (97)	33 (97)	NA
Completers Sample, N (%)	35 (95)	31 (91)	272 (77)
Safety Set, N (%)	37 (100)	34 (100)	354 (100)

CSR = Clinical Study Report; IR = immediate-release; LCIG = levodopa/carbidopa intestinal gel; NA = not applicable; NR = not reported; OLC = oral levodopa/carbidopa; PBO = placebo.

[a] Study 004 was an open-label, non-comparative trial that enrolled 354 patients.

Source: Study 001/002 CSR.[26] Olanow et al. (2014).[27] Fernandez et al. (2015).[28]

Exposure to Study Treatments

Double-Blind, Randomized Controlled Trial (Study 001/002)

Details about exposure in Study 001/002 are provided in Table 10 and Table 11.

Patients had their levodopa doses titrated for a mean of approximately seven to eight days (SD: 2.5) in the screening phase, during which the average mean daily levodopa dose was 1,096.5 mg (SD: 438.3). By the end of the titration phase, patients in the LCIG + PBO IR OLC capsules group were treated with less levodopa (1,127.6) mg [SD: 531.8]) than patients in the PBO LCIG + IR OLC capsules group versus (1,400.0 mg [SD: 698.5]).

Patients were treated for a mean of approximately 80 days in the DB treatment phase, during which the average mean daily levodopa dose was less in the LCIG + PBO IR OLC capsules group (1,117.3 mg [SD: 473.7]) compared with the PBO LCIG + IR OLC capsules group (1,350.6 mg [SD: 617.9]). By the end of the DB treatments phase, patients in the LCIG + PBO IR OLC capsules group were treated with less levodopa (1,131.1 mg [SD 435.1]) than patients in the PBO LCIG + IR OLC capsules group (1,374.1 mg [SD: 615.0]).

The majority of patients used rescue medication on valid diary days. The proportion of patients requiring rescue medication was similar between groups throughout the study

(97% in the LCIG + PBO IR OLC capsules group versus 91% in the PBO LCIG + IR OLC capsules group). Overall, fewer patients in the LCIG + PBO IR OLC capsules group (37%) required rescue medication at week 12 compared with the PBO LCIG + IR OLC capsules group (42%). Patients mostly required ≤ 14 days of rescue medication during the study across both treatment groups (72% in the LCIG + PBO IR OLC capsules group versus 65% in the PBO LCIG + IR OLC capsules group). The average mean doses of rescue IR OLC during the study were similar between treatment groups (180.6 mg [SD: 156.2] in the LCIG + PBO IR OLC capsules group versus 139.8 [SD: 81.3] in the PBO LCIG + IR OLC capsules group). Conversely, mean doses of rescue medication at week 12 were lower in the LCIG + PBO IR OLC capsules group (115.3 mg [SD: 67.8]) compared with the PBO LCIG + IR OLC capsules group (210.3 mg [SD: 201.3]).

Replacement mean IR OLC doses due to study drug interruptions were smaller in the LCIG + PBO IR OLC capsules group (302.8 mg [SD: 243.7]) compared with the PBO LCIG + IR OLC capsules group (431.8 mg [SD: 494.1]), whereas night-time IR OLC doses were similar between the two groups (126.1 mg [SD: 60.5] in the LCIG + PBO IR OLC capsules group versus 132.9 mg [SD 104.0] in the PBO LCIG + IR OLC capsules group).

Overall compliance with treatment (defined as between ≥ 80% and ≤ 120% compliance at each visit with available data) was 89% for the LCIG group and 81% for the PBO IR OLC capsules group in the LCIG + PBO IR OLC capsules group and 97% for the PBO LCIG and 76% for the IR OLC capsules in the PBO LCIG + IR OLC capsules group. Details regarding treatment compliance in Study 001/002 are provided in Table 12.

Open-Label, Non-Comparative Study (Study 004)

Patients were treated with a mean of 1,082.9 mg of levodopa daily at screening. Patients were subsequently optimized to mean daily doses of 1,547.4 mg by the last day of the titration periods over a mean of 4.5 (2.2) days. During the treatment phase, mean daily levodopa doses ranged between 1,551.0 mg and 1,630.5 mg. Among the 28% patients receiving daily dose of IR OLC during the treatment phase, the mean daily dose during the night was174.6 mg.

The minority of patients (28%) were not receiving concomitant PD medications during Study 004, whereas, approximately half (52%) were taking one PD medication. The majority (68%) of patients were treated with levodopa or derivatives and approximately half (49%) were treated with levodopa only. Details pertaining to concomitant medication during Study 004 are presented in Table 13.

Table 10: Summary of Treatment Exposure

Exposure	Study 001/002 (Safety Set)		Study 004
	LCIG + PBO IR OLC Capsules N = 37	PBO LCIG + IR OLC Capsules N = 34	LCIG N = 354
Screening Phase			
Average daily levodopa dose			
Mean dose, mg (SD)	1,029.1 (386.3)	1,169.9 (483.7)	1,082.9 (582.1)
Median dose, mg (min, max)	950.0 (500, 2,125)	1,200.0 (400, 2,100)	NR
Daily levodopa at the last day of initial titration			
Mean dose, mg (SD)	1,127.6 (531.8)	1,400.0 (698.5)	1,547.4 (NR)
Median dose, mg (min, max)	1,020.0 (460, 3,452)	1,400.0 (500, 3,700)	NR
Duration of titration			
Mean days, (SD)	7.1 (2.5)	8.0 (2.5)	4.5 (2.2)
Median days, (min, max)	6.0 (1, 15)	8.0 (2, 16)	NR
Treatment Phase			
Average daily levodopa dose			
Mean dose, mg (SD)	1,117.3 (473.7)	1,350.6 (617.9)	1,551.0 to 1,630.5 (NR)
Median dose, mg (min, max)	1,013.4 (632, 2,983)	1,290.8 (558, 3,096)	NR
Daily levodopa dose at last study visit[a]			
Mean dose, mg (SD)	1,131.1 (435.1)	1,374.1 (615.0)	1,572.4 (NR)
Median dose, mg (min, max)	1,116.0 (597, 2,528)	1,266.7 (550, 2,800)	
Number of days on treatment			
Mean days, (SD)	82.3 (18.2)	78.7 (22.9)	NR
Median days, (min, max)	86.0 (2, 94)	85.0 (2, 97)	NR

CSR = Clinical Study Report; IR = immediate-release; LCIG = levodopa/carbidopa intestinal gel; max = maximum; min = minimum; NR = not reported; OLC = oral levodopa/carbidopa; PBO = placebo; SD = standard deviation.

Note: For LCIG, the dose of levodopa is calculated by multiplying the amount of LCIG infused through a PEG-J tube (mL) by 20 mg/mL. For levodopa/carbidopa capsules, the dose of levodopa is calculated by multiplying the number of capsules times 100 mg.

Note: Daily dose is the sum of morning dose, continuous maintenance dose, and the 60 mg dose received when the 3 mL prime is flushed from the tubing.

[a] Based on the completers sample, which included 35 patients in the intestinal gel group and 31 patients in the IR group.

Source: Study 001/002 CSR,[26] Fernandez et al. (2015).[28]

Table 11: Summary of Treatment Exposure Other Than Study Drugs (Safety Set)

Exposure	Study 001/002		Study 004
	LCIG + PBO IR OLC Capsules N = 37	PBO LCIG + IR OLC Capsules N = 34	LCIG N = 354
IR OLC Rescue Therapy			
Patients who required rescue medication any time during the study, n (%)	36 (97)	31 (91)	NR
Patients who required rescue medication at week 12, n (%)	13 (37)	13 (42)	NR
Days of Rescue Medication During the Study, n (%)			
1 day to 7 days	14 (39)	15 (48)	NR
8 days to 14 days	12 (33)	5 (16)	NR
15 days to 28 days	5 (14)	4 (13)	NR
29 days to 42 days	2 (6)	0	NR
43 days to 56 days	1 (3)	2 (7)	NR
57 days to 70 days	1 (3)	3 (10)	NR
≥ 71 days	1 (3)	2 (7)	NR
Average Daily Rescue Levodopa			
Mean dose, mg (SD)	139.8 (81.3)	180.6 (156.2)	NR
Median dose, mg (min, max)	109.6 (58.6, 433.3)	133.3 (50.0, 816.7)	NR
Mean daily rescue levodopa at week 12, mg (SD)	115.3 (67.8)	210.3 (201.3)	NR
Average Capsules of Rescue Medication During the DB Treatment Phase, n (%)[a]			
0 capsules per day	11 (31)	12 (39)	NR
0 < capsules per ≤ 0.5	20 (57)	11 (35)	NR
0.5 < capsules per ≤ 1	2 (6)	7 (23)	NR
1 < capsules per ≤ 2	2 (6)	0	NR
4 < capsules per day ≤ 5	0	1 (3)	NR
IR OLC Night-Time Therapy	N = 25	N = 19	
Average Daily Levodopa			
Mean dose, mg (SD)	126.1 (60.5)	132.9 (104.0)	174.6 (NR)
Median dose, mg (min, max)	100.0 (50.0, 300.0)	106.3 (50.0, 525.0)	NR
IR OLC Replacement[b]	N = 18	N = 14	
Average Daily Levodopa			
Mean dose, mg (SD)	302.8 (243.7)	431.8 (494.1)	NR
Median dose, mg (min, max)	200.0 (50.0, 800.0)	170.5 (50.0, 1466.7)	NR

CSR = Clinical Study Report; DB = double-blind; IR = immediate-release; LCIG = levodopa/carbidopa intestinal gel; max = maximum; min = minimum; NR = not reported; OLC = oral levodopa/carbidopa; PBO = placebo; SD = standard deviation.

Note: The average rescue medication dose is calculated as the sum of the dose taken on all days during the study week divided by the number of days rescue medication was needed during the study week.

Note: For LCIG, the dose of levodopa is calculated by multiplying the amount of LCIG infused through a PEG-J tube (mL) by 20 mg/mL. For levodopa/carbidopa capsules, the dose of levodopa is calculated by multiplying the number of capsules times 100 mg.

Note: Daily dose is the sum of morning dose, continuous maintenance dose, and the 60 mg dose received when the 3 mL prime is flushed from the tubing.

[a] Based on the completers' sample, which included 35 patients in the intestinal gel group and 31 patients in the IR group.

[b] IR OLC replacement therapy was used if infusion was interrupted.

Source: Study 001/002 CSR,[26] Fernandez et al. (2015).[28]

Table 12: Summary of Treatment Compliance

Compliance	Study 001/002			
	LCIG + PBO IR OLC Capsules N = 37		PBO LCIG + IR OLC Capsules N = 34	
	LCIG	PBO IR OLC Capsules	PBO LCIG	IR OLC Capsules
Overall compliance, n (%)	33 (89)	30 (81)	33 (97)	26 (76)

IR = immediate-release; LCIG = levodopa/carbidopa intestinal gel; OLC = oral levodopa/carbidopa; PBO = placebo.

Note: Compliance for the gel for infusion is based on the number of hours the portable infusion pump was turned on relative to the protocol-defined goal of 16 hours per day. Compliance for capsules is based on the number of capsules actually taken during the visit relative to the number of capsules prescribed during the visit.

Note: Patients were considered compliant overall if they were between ≥ 80% and ≤ 120% compliant at each visit with available data.

Source: Study 001/002 Clinical Study Report.[26]

Table 13: Concomitant Parkinson Disease Medications in Study 004

Concomitant PD Medication	Total (N = 324)
No concomitant PD medication	90 (28)
Levodopa/carbidopa only	158 (49)
Levodopa or derivatives	219 (68)
Dopamine agonists	41 (13)
Amantadine	31 (10)
COMT inhibitors	12 (4)
MAO-B inhibitors	5 (2)
Number of Concomitant PD Medication Classes Received	
One	169 (52)
Two	55 (17)
Three or more	10 (3)

COMT = catechol-O-methyltransferase; MAO-B = monoamine oxidase B; PD = Parkinson disease.

Source: Fernandez et al. (2015).[28]

Critical Appraisal

Double-Blind, Randomized Controlled Trial (Study 001/002)

Internal Validity

Study 001/002 was designed as a DB, active-controlled RCT that used appropriate methods to randomize patients (i.e., IVRS) and conceal treatment allocation. The objective of Study 001/002 was to assess the efficacy and safety of LCIG based on a primary end point of change from baseline to 12 weeks in normalized “off” time.

Although randomization appeared to be successful, patients experienced less “off” time and more “on” time at baseline in the LCIG + PBO IR OLC capsules group, which may indicate less severe PD. Patients with more severe PD (i.e., the PBO LCIG + IR OLC capsules group) may not benefit from treatment to the same extent as those with less severe disease, which could result in the overestimation of treatment effect associated with LCIG

therapy. However, the clinical expert consulted for this CDR review suggested that any such bias is unlikely to explain the magnitude of the treatment effect.

Overall compliance with the active IR OLC capsules in the PBO LCIG + IR OLC capsules group was 76%. Therefore, patients who were not compliant with the IR OLC capsules in this treatment group would not be receiving any levodopa therapies (i.e., only receiving PBO LCIG). Given that the symptoms of PD are well known (i.e., “off” state symptoms, such as tremors or immobility) and that non-compliant patients may have experienced symptoms of uncontrolled PD, some patients may have been inadvertently unblinded to treatment status. Unblinding may lead to biases in the reporting of subjective outcomes (i.e., “on” and “off” states, HRQoL, and AEs).

Study 001/002 was designed as a superiority trial; therefore, analyses should ideally be conducted in an intention-to-treat (ITT) population. However, all efficacy analyses were conducted using the FAS population, defined as all randomly allocated participants with data for baseline and at least one post-baseline assessment. The exclusion of patients is inconsistent with the true definition of an ITT analysis, in which all randomized participants are included. However, given the small number of exclusions (one patient in each group), the potential for bias is not of concern.

In the adjusted ANCOVA model used in the primary analysis, missing data were imputed using the LOCF approach. To assess the robustness of the treatment effect, sensitivity analyses were conducted using different covariates in the ANCOVA model and different methods to impute missing data (MMRM).

Study 001/002 included multiple end points based on change in “off” and “on” time captured by means of PDHDs. All patients were trained in the completion of the diary by an instructional DVD and were required to demonstrate 75% completion and concordance with the investigators, leading to more consistent results. Patients who were unable to complete their diaries had their caregivers complete the entries on their behalf. The level of agreement between patients’ and their caregivers’ perceptions of “off” time and “on” time was not assessed in this trial and remains unclear.

A statistical testing hierarchy to control for type I error was used to examine secondary outcomes. Subsequent to the statistical significance (at alpha = 0.05 level) of the primary efficacy variable, a testing hierarchy was performed on the secondary efficacy variables. The statistical testing hierarchy stopped when an end point was found not to be statistically significant at the alpha = 0.05 level. However, the manufacturer does not appear to have adhered to its pre-specified testing strategy by continuing statistical testing for superiority after statistical insignificance was established. Overall, statistical testing should have stopped after the change in the UPDRS Part III end point (fifth in the order of secondary analyses). It is important to note that statistical inference should only be made for the outcomes up to and including the UPDRS Part III. No statistical inference can be made for EQ-5D-3L and ZBI end points even though they were included in the in the statistical testing hierarchy because they were conducted subsequent to the failure of a prior end point.

All other outcomes, including “on” time without dyskinesia, “on” time with non-troublesome dyskinesia, “on” time with troublesome dyskinesia, domain scores of the PDQ-39 (mobility, ADL, emotional well-being, stigma, social support, cognition, communication, and bodily discomfort), Part I and Part IV of the UPDRS (including the sum of Part I, II, and III) as well as the EQ VAS were not included in the statistical testing hierarchy and not adjusted for

multiplicity. Therefore, there is a risk of type I error. As such, the results should only be considered hypothesis-generating.

External Validity

Study 001/002 was multinational; however, it did not include any sites or patients from Canada. Overall, 27% of patients were screening failures, mostly due to protocol violations. Stringent inclusion and exclusion criteria can result in large number of screening failures and can potentially lead to the inclusion of a select population that may not be completely representative of the advanced PD population in Canada. This can potentially limit the generalizability of the trial results. Despite the large number of screening failures, the clinical experts consulted by CDR for this review highlighted that Study 001/002 appears to have recruited patients with characteristics similar to those with advanced PD who would be considered eligible for treatment with LCIG.

Furthermore, patients were required to have at least 75% concordance with investigator rating and at least 75% compliance in completion of the PDHD to meet the inclusion criteria of the study. Including only those who demonstrate agreement with the investigator in the completion of the PDHD can also lead to the inclusion of a select population that may not be completely representative of the advanced PD population in Canada. This can also potentially limit the generalizability of the trial results.

The evaluation of "off" time as the primary end point (identified as among the most important end points by the patient groups who provided input for this CDR submission) was supported by the evaluation of a key secondary end point: "on" time without troublesome dyskinesia (a composite of "on" time without dyskinesia and "on" time with non-troublesome dyskinesia). The FDA considers improvement in functional "on" time to be the most important end point for treating patients with motor fluctuations; it is also said to provide a better indication of improvement in patient functioning compared with "off" time.[53,67,68] Furthermore, the patient input submitted for this review also highlighted the importance of "on" time as a desirable outcome.

Overall, Study 001/002 was relatively short in duration (12 weeks) considering that PD therapies would be expected to continue for a patient's lifetime. However, patients enrolled in Study 001/002 were provided the opportunity to continue treatment in a 12-month, open-label, safety extension study (Study 003) providing longer-term safety and efficacy associated with LCIG therapy (Appendix 6).

Open-Label, Non-Comparative Study (Study 004)

Internal Validity

There are several limitations to the long-term, open-label, non-randomized, non-comparative safety trial Study 004. First, given that this was an uncontrolled study, it remains unclear whether the changes observed in the safety and efficacy profile were due to a natural course of the disease or to long-term treatment with LCIG through a PEG-J tube. Open-label trial designs in which both the investigators and the participants are not blinded to treatment allocation may have an impact on subjective outcomes, such as some of the patient-reported AEs, and on outcomes related to efficacy and HRQoL. Reporting of "off" and "on" time is also subjective; therefore, it is subject to bias. In addition, during Study 004, patients were able to continue concomitant anti-PD medication; this makes it difficult to ascertain the safety and efficacy of the intervention in isolation. Also of note, data were incomplete for some outcomes, which may increase the potential for bias in the patient-

reported outcomes if those with complete data had more favourable responses. Further, adjustments for multiple comparisons were not performed for the efficacy outcomes; thus, the risk of type I error is introduced.

External Validity

Study 004 was multinational and included sites and patients from Canada. Overall, 16% of patients were screening failures; however, the most common reasons were not provided. Stringent inclusion and exclusion criteria can result in large screening failures and can potentially lead to the inclusion of a select population that may not be completely representative of the advanced PD population in Canada, potentially limiting the generalizability of the trial results. Despite the large screening failures, Study 004 appears to have recruited patients with characteristics similar to those included in Study 001/002, who were identified as being representative of those with advanced PD and would be considered eligible for treatment with LCIG.

Overall, 354 patients in Study 004 were treated with LCIG through a PEG-J tube and followed for 54 weeks, making Study 004 the largest open-label, non-comparative safety study available. Considering that PD therapies would be expected to continue for a patient's lifetime, the duration and sample size of Study 004 can provide important information with respect to the long-term harms profile.

Efficacy

Only those efficacy outcomes identified in the review protocol are reported in Table 4. See Appendix 4 for detailed efficacy data.

"Off" Time

Double-Blind, Randomized Controlled Trial (Study 001/002)

Compared with IR OLC capsules, the LCIG group had a statistically significant reduction in daily normalized "off" time at week 12 (the primary outcome). The adjusted LSMD in change from baseline was –1.91 hours (95% CI, –3.05 to –0.76; *P* = 0.0015) in favour of LCIG. Details regarding the primary outcomes in Study 001/002 are provided in Table 14. The results of the sensitivity analyses of the primary outcome were based on MMRM for imputed data and ANCOVA models (without covariate of rescue medication on valid PDHD days, with covariate of rescue medication over the treatment period, with values on final PDHD days, with rescue medication use replaced by average daily normalized "off" time at baseline, and excluding values on final PDHD days with rescue medication use). These results were consistent with the primary analysis (Table 22).

Daily absolute "off" time at week 12 was also evaluated and was consistent with the results of the primary analysis (normalized "off" time at week 12). Details regarding the absolute change in daily "off" time at week 12 in Study 001/002 are provided in Table 23.

Although the study protocol indicated that the analyses of the primary end point would be performed in the subgroups of patients with PD for ≤ 10 years and ≥ 10 years, the analyses were not provided in the manufacturer-submitted materials.

Open-Label, Non-Comparative Study (Study 004)

Overall, the mean amount of "off" time decreased from baseline to the last study visit (–4.4 hours [SD: 2.9], $P < 0.001$). Details pertaining to the change in "off" time during Study 004 are presented in Table 14. The "off" time end point in Study 004 was not corrected for multiple statistical testing.

Table 14: Summary of "Off" Time

End Point	Study 001/002 (FAS)		Study 004
	LCIG + PBO IR OLC Capsules N = 36	PBO LCIG + IR OLC Capsules N = 33	LCIG N = 354
"Off" Time, Hours Per Day			
Baseline, n (%)	35 (97)	31 (94)	316 (87)
Baseline, mean (SD)	6.32 (1.72)	6.90 (2.06)	6.75 (2.35)
Adjusted LS mean change from baseline at last study visit (SE)	–4.04 (0.65)	–2.14 (0.66)	–4.4 (2.9), $P < 0.001$[a]
Adjusted LS mean difference in change from baseline versus comparator (95% CI)	–1.91 (–3.05 to –0.76), $P = 0.0015$		NA

ANCOVA = analysis of covariance; CI = confidence interval; CSR = Clinical Study Report; FAS = full analysis set; IR = immediate-release; LCIG = levodopa/carbidopa intestinal gel; LOCF = last observation carried forward; LS = least squares; NA = not applicable; OLC = oral levodopa/carbidopa; PBO = placebo; SD = standard deviation; SE = standard error.

Note: The diary is completed every 30 minutes for the full 24 hours of each of 3 days prior to selected clinic visits. It reflects both time awake and time asleep. Daily totals are normalized to a 0-hour to 16-hour scale (i.e., 16 hours of awake time). The normalized totals for the 3 days prior to the visit are averaged for the analysis.

Note: Treatment comparisons are based on an ANCOVA model, including effects for treatment and country and using the corresponding baseline and the natural logarithm of the mean daily dose of rescue medication on valid symptom diary days as covariates.

Note: LOCF was used to impute missing data.

[a] Unadjusted mean change from baseline at last study visit. SD instead of SE. End point not corrected for multiple statistical testing.

Source: Study 001/002 CSR,[26] Olanow et al. (2014)[27] Fernandez et al. (2015).[28]

"On" Time

Double-Blind, Randomized Controlled Trial (Study 001/002)

Compared with IR OLC capsules, the LCIG group had a statistically significant improvement in daily normalized "on" time without troublesome dyskinesia at week 12 (the key secondary outcome). The adjusted LSMD in change from baseline was 1.86 hours (95% CI, 0.56 to 3.17; $P = 0.0059$) in favour of LCIG. This end point was driven by two components: daily normalized "on" time without dyskinesia and daily normalized "on" time with non-troublesome dyskinesia (adjusted LSMD in change from baseline were 2.28 [95% CI, 0.47 to 4.09; $P = 0.0142$] and –0.73 [95% CI, –2.22 to 0.76; $P = 0.3294$], respectively). No statistically significant differences were reported in daily normalized "on" time with troublesome dyskinesia (adjusted LSMD in change from baseline: –0.08 [95% CI, –0.98 to 0.82; $P = 0.8574$]). Details regarding "on" time in Study 001/002 are provided in Table 15.

Daily absolute "on" time at week 12 was also evaluated and was consistent with the results of the secondary analyses (normalized "on" time at week 12). Details regarding the absolute change in daily "on" time at week 12 in Study 001/002 are provided in Table 23.

Open-Label, Non-Comparative Study (Study 004)

The mean amount of "on" time without troublesome dyskinesia increased from baseline to the last study visit (4.8 hours [SD: 3.4], $P < 0.001$), whereas the mean amount of "on" time with troublesome dyskinesia decreased from baseline to the last study visit (–0.4 hours [SD: 2.8], $P = 0.023$). Results for "on" time without dyskinesia and daily normalized "on" time with non-troublesome dyskinesia were not reported. Details pertaining to the change in "on" time during Study 004 are presented in Table 15. The "on" time end points in Study 004 were not corrected for multiple statistical testing.

Table 15: Summary of "On" Time

End Point	Study 001/002 (FAS)		Study 004
	LCIG + PBO IR OLC Capsules N = 36	PBO LCIG + IR OLC Capsules N = 33	LCIG N = 354
"On" Time Without Troublesome Dyskinesia, Hours Per Day			
Baseline, n (%)	35 (97)	31 (94)	316
Baseline, mean (SD)	8.70 (2.01)	8.04 (2.09)	7.65 (2.45)
Adjusted LS mean change from baseline at last study visit (SE)	4.11 (0.75)	2.24 (0.76)	4.8 (3.4), $P < 0.001$[b]
Adjusted LS mean difference in change from baseline versus comparator (95% CI)	1.86 (0.56 to 3.17), $P = 0.0059$		NA
"On" Time Without Dyskinesia, Hours Per Day[a]			
Baseline, n (%)	35 (97)	31 (94)	NR
Baseline, mean (SD)	6.37 (2.71)	5.73 (3.05)	NR
Adjusted LS mean change from baseline at last study visit (SE)	3.37 (1.04)	1.09 (1.05)	NR
Adjusted LS mean difference in change from baseline versus comparator (95% CI)	2.28 (0.47 to 4.09), $P = 0.0142$		NA
"On" Time With Non-Troublesome Dyskinesia, Hours Per Day[a]			
Baseline, n (%)	35 (97)	31 (94)	NR
Baseline, mean (SD)	2.33 (1.81)	2.31 (2.16)	NR
Adjusted LS mean change from baseline at last study visit (SE)	0.81 (0.86)	1.54 (0.86)	NR
Adjusted LS mean difference in change from baseline versus comparator (95% CI)	–0.73 (–2.22 to 0.76), $P = 0.3294$		NA
"On" Time With Troublesome Dyskinesia, Hours Per Day[a]			
Baseline, n (%)	35 (97)	31 (94)	307
Baseline, mean (SD)	0.97 (1.63)	1.05 (1.51)	1.61 (2.03)
Adjusted LS mean change from baseline at last study visit (SE)	–0.11 (0.52)	–0.03 (0.52)	–0.4 (2.8), $P = 0.023$[b]
Adjusted LS mean difference in change from baseline versus comparator (95% CI)	–0.08 (–0.98 to 0.82), $P = 0.8574$		NA

ANCOVA = analysis of covariance; CI = confidence interval; CSR = Clinical Study Report; FAS = full analysis set; IR = immediate-release; LCIG = levodopa/carbidopa intestinal gel; LS = least squares; NA = not applicable; NR = not reported; OLC = oral levodopa/carbidopa; PBO = placebo; SD = standard deviation; SE = standard error.

Note: The diary is completed every 30 minutes for the full 24 hours of each of 3 days prior to selected clinic visits. It reflects both time awake and time asleep. Daily totals are normalized to a 0-hour to 16-hour scale (i.e., 16 hours of awake time). The normalized totals for the 3 days prior to the visit are averaged for the analysis.

Note: Treatment comparisons are based on an ANCOVA model including effects for treatment and country and using the corresponding baseline as covariates.

[a] Individual outcomes were not part of the statistical testing hierarchy.

[b] Unadjusted mean change from baseline at last study visit. SD instead of SE. End point not corrected for multiple statistical testing.

Source: Study 001/002 CSR,[26] Olanow et al. (2014),[27] Fernandez et al. (2015).[28]

39-Item Parkinson's Disease Questionnaire

Double-Blind, Randomized Controlled Trial (Study 001/002)

Compared with IR OLC capsules, the LCIG group had a statistically significant reduction in the PDQ-39 summary index score. The adjusted LSMD in change from baseline was –7.0 (95% CI, –12.6 to –1.4; *P* = 0.0155) in favour of LCIG. Details regarding the PDQ-39 summary index score and its subscales (not adjusted for multiple statistical testing) in Study 001/002 are provided in Table 16.

Open-Label, Non-Comparative Study (Study 004)

The change from baseline at the final study visit in the PDQ-39 summary index score was –6.9 (14.1, *P* < 0.001). Details pertaining to the change in PDQ-39 scores and subscales during Study 004 are presented in Table 16. The PDQ-39 end points in Study 004 were not corrected for multiple statistical testing.

Table 16: Summary of 39-Item Parkinson's Disease Questionnaire

End Point	Study 001/002 (FAS)		Study 004
	LCIG + PBO IR OLC Capsules N = 36	PBO LCIG + IR OLC Capsules N = 33	LCIG N = 354
Summary Index Score			
Baseline, n (%)	36 (100)	33 (100)	320 (90)
Baseline, mean (SD)	35.1 (18.0)	38.6 (17.9)	42.7 (15.0)
Adjusted LS mean change from baseline at last study visit (SE)	–10.9 (3.3)	–3.9 (3.2)	-6.9 (14.1), *P* < 0.001[b]
Adjusted LS mean difference in change from baseline versus comparator (95% CI)	–7.0 (–12.6, –1.4), *P* = 0.0155		NA
Mobility[a]			
Baseline, n (%)	36 (100)	33 (100)	317 (90)
Baseline, mean (SD)	45.7 (26.0)	55.0 (23.7)	58.8 (22.8)
Adjusted LS mean change from baseline at last study visit (SE)	–17.3 (5.0)	–6.8 (4.9)	–11.2 (23.4) *P* < 0.001[b]
Adjusted LS mean difference in change from baseline versus comparator (95% CI)	–10.4 (–19.1 to –1.8), *P* = 0.0184		NA
Activities of Daily Living[a]			
Baseline, n (%)	36 (100)	33 (100)	317 (90)
Baseline, mean (SD)	39.7 (24.6)	43.4 (23.0)	50.7 (22.3)
Adjusted LS mean change from baseline at last study visit (SE)	–12.9 (5.3)	–1.3 (5.2)	–8.3 (22.6) *P* < 0.001[b]
Adjusted LS mean difference in change from baseline versus comparator (95% CI)	–11.6 (–20.6 to –2.5), *P* = 0.0129		NA
Emotional Well-Being[a]			
Baseline, n (%)	36 (100)	33 (100)	317 (90)
Baseline, mean (SD)	31.7 (17.3)	3.2 (23.4)	39.4 (21.8)
Adjusted LS mean change from baseline at last study visit (SE)	–7.1 (4.0)	–4.9 (4.0)	–4.2 (19.7), *P* < 0.001[b]
Adjusted LS mean difference in change from baseline versus comparator (95% CI)	–2.2 (–9.0 to 4.6), *P* = 0.5246		NA

End Point	Study 001/002 (FAS)		Study 004
	LCIG + PBO IR OLC Capsules N = 36	PBO LCIG + IR OLC Capsules N = 33	LCIG N = 354
Stigma[a]			
Baseline, n (%)	36 (100)	33 (100)	317 (89)
Baseline, mean (SD)	26.4 (26.5)	28.8 (26.3)	32.5 (26.0)
Adjusted LS mean change from baseline at last study visit (SE)	–8.9 (4.4)	–4.5 (4.4)	–9.1 (22.1), $P < 0.001$[b]
Adjusted LS mean difference in change from baseline versus comparator (95% CI)	–4.5 (–12.0 to 3.1), $P = 0.2423$		NA
Social Support[a]			
Baseline, n (%)	36 (100)	33 (100)	315 (90)
Baseline, mean (SD)	18.1 (24.0)	13.4 (20.0)	17.2 (19.7)
Adjusted LS mean change from baseline at last study visit (SE)	–3.9 (3.5)	–0.1 (3.6)	–0.3 (18.9), $P < 0.001$[b]
Adjusted LS mean difference in change from baseline versus comparator (95% CI)	–3.8 (–9.9 to 2.4), $P = 0.2243$		NA
Cognition[a]			
Baseline, n (%)	36 (100)	33 (100)	317 (90)
Baseline, mean (SD)	24.8 (16.9)	29.0 (22.5)	27.2 (18.6)
Adjusted LS mean change from baseline at last study visit (SE)	–7.3 (4.0)	–3.2 (3.9)	–4.5 (18.0), $P < 0.001$[b]
Adjusted LS mean difference in change from baseline versus comparator (95% CI)	–4.0 (–10.8 to 2.8), $P = 0.2407$		NA
Communication[a]			
Baseline, n (%)	36 (100)	33 (100)	317 (90)
Baseline, mean (SD)	30.8 (23.2)	28.8 (23.8)	34.3 (20.4)
Adjusted LS mean change from baseline at last study visit (SE)	–9.5 (4.1)	4.4 (4.1)	–3.9 (19.4), $P < 0.001$[b]
Adjusted LS mean difference in change from baseline versus comparator (95% CI)	–13.8 (–20.8 to –6.8), $P = 0.0002$		NA
Bodily Discomfort[a]			
Baseline, n (%)	36 (100)	33 (100)	317 (90)
Baseline, mean (SD)	45.4 (26.5)	42.4 (24.4)	46.2 (22.9)
Adjusted LS mean change from baseline at last study visit (SE)	–13.5 (6.1)	–10.2 (6.0)	–5.8 (22.4), $P < 0.001$[b]
Adjusted LS mean difference in change from baseline versus comparator (95% CI)	–3.3 (–13.6 to 6.9), $P = 0.5213$		NA

ANCOVA = analysis of covariance; CSR = Clinical Study Report; CI = confidence interval; FAS = full analysis set; IR = immediate-release; LCIG = levodopa/carbidopa intestinal gel; LS = least squares; NA = not applicable; OLC = oral levodopa/carbidopa; PBO = placebo; PDQ-39 = 39-item Parkinson's Disease Questionnaire; SD = standard deviation; SE = standard error.

Note: The PDQ-39 summary index is the sum of all answers divided by the highest score possible (i.e., number of answers multiplied by 4), which is multiplied by 100 to place the score on a scale of 0 to 100. Higher scores are associated with more severe symptoms.

Note: Treatment comparisons are based on an ANCOVA model, including effects for treatment and country and using the corresponding baseline as covariates.

[a] Individual subscales of the PDQ-39 were not part of the statistical testing hierarchy.

[b] Unadjusted mean change from baseline at last study visit. SD instead of SE. End point not corrected for multiple statistical testing.

Source: Study 001/002 CSR,[26] Olanow et al. (2014),[27] Fernandez et al. (2015).[28]

Clinical Global Impression – Improvement

Double-Blind, Randomized Controlled Trial

Compared with IR OLC capsules, the LCIG group had a statistically significant reduction in the CGI-I. The adjusted LS mean difference in change from baseline was –0.7 (95% CI, –1.4 to –0.1; *P* = 0.0258) in favour of LCIG. Details regarding the CGI-I score in Study 001/002 are provided in Table 17.

Open-Label, Non-Comparative Study (Study 004)

CGI-I scores were not reported. Overall, the majority of patients (92%) improved, 3% did not change, and 4% worsened in the

CGI-I score from baseline to the last study visit. Details pertaining to the change in CGI-I scores during Study 004 are presented in Table 17. The CGI-I end points in Study 004 were not corrected for multiple statistical testing.

Table 17: Summary of Clinical Global Impression – Improvement (Full Analysis Set)

End Point	Study 001/002		Study 004
	LCIG + PBO IR OLC Capsules N = 36	PBO LCIG + IR OLC Capsules N = 33	LCIG N = 354
CGI-I Score			
Baseline, n (%)	36 (100)	33 (100)	316
Baseline, mean (SD)[a]	4.2 (0.7)	4.6 (0.8)	4.85 (0.8)
Adjusted LS mean change from baseline at last study visit (SE)	2.3 (0.4)	3.0 (0.4)	NR
Adjusted LS mean difference in change from baseline versus comparator (95% CI)	–0.7 (–1.4 to –0.1), *P* = 0.0258		NA
CGI-I Items	NR	NR	
Very much improved	NR	NR	22%
Much improved	NR	NR	56%
Minimally improved	NR	NR	14%
No change	NR	NR	3%
Minimally worse	NR	NR	3%
Much worse	NR	NR	1%
Very much worse	NR	NR	0%

ANCOVA = analysis of covariance; CGI-I = Clinical Global Impression – Improvement; CGI-S = Clinical Global Impression – Severity; CI = confidence interval; CSR = Clinical Study Report; FAS = full analysis set; IR = immediate-release; LCIG = levodopa/carbidopa intestinal gel; LS = least squares; NA = not applicable; NR = not reported; OLC = oral levodopa/carbidopa; PBO = placebo; SD = standard deviation; SE = standard error.

Note: The CGI-S is a global assessment by the investigator of current symptomatology and impact of illness on functioning. The ratings of the CGI-S are as follows: 1 = normal, 2 = borderline ill, 3 = mildly ill, 4 = moderately ill, 5 = markedly ill, 6 = severely ill, and 7 = among the most extremely ill.

Note: The CGI-I is a global assessment by the investigator of the change in clinical status since the start of treatment. The CGI-I ratings are as follows: 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, 7 = very much worse.

Note: Treatment comparisons are based on an ANCOVA model including effects for treatment, country, and with the CGI-S as a covariate.

[a] Baseline scores are based on the CGI-S score.

Source: Study 001/002 CSR,[26] Olanow et al. (2014),[27] Fernandez et al. (2015).[28]

Unified Parkinson's Disease Rating Scale

Double-Blind, Randomized Controlled Trial

Compared with IR OLC capsules, the LCIG group had a statistically significant reduction in the UPDRS Part II score. The adjusted LSMD in change from baseline was –3.0 (95% CI, –5.3 to –0.8; *P* = 0.0086) in favour of LCIG. Conversely, no statistically significant difference in the UPDRS Part III score was reported. The adjusted LSMD in change from baseline was 1.4 (95% CI, –2.8 to 5.6; *P* = 0.5020). Details regarding the UPDRS and its individual parts in Study 001/002 are provided in Table 18. (Only parts II and III were adjusted for multiple statistical testing.)

Open-Label, Non-Comparative Study (Study 004)

Overall, UPDRS II scores decreased from baseline to the last study visit (–4.4 [SD 6.5], *P* < 0.001). Other UPDRS score values were not reported. Details pertaining to the change in UPDRS scores during Study 004 are presented in Table 18. The UPDRS end points in Study 004 were not corrected for multiple statistical testing.

Table 18: Summary of Unified Parkinson's Disease Rating Scale

End Point	Study 001/002 (FAS)		Study 004
	LCIG + PBO IR OLC Capsules N = 36	PBO LCIG + IR OLC Capsules N = 33	LCIG N = 354
UPDRS Total Score (Part I, II, III)[a]			
Baseline, n (%)	36 (100)	33 (100)	292
Baseline, mean (SD)	31.5 (15.6)	35.8 (18.9)	48.4 (18.9)
Adjusted LS mean change from baseline at last study visit (SE)	–3.6 (3.4)	–2.1 (3.4)	NR
Adjusted LS mean difference in change from baseline versus comparator (95% CI)	–1.5 (–7.4 to 4.4), *P* = 0.6088		NA
UPDRS Part I Score[a]			
Baseline, n (%)	36 (100)	33 (100)	NR
Baseline, mean (SD)	1.8 (1.7)	1.8 (1.8)	NR
Adjusted LS mean change from baseline at last study visit (SE)	–0.2 (0.4)	–0.5 (0.4)	NR
Adjusted LS mean difference in change from baseline versus comparator (95% CI)	0.3 (–0.4 to 0.9), *P* = 0.3741		NA
UPDRS Part II Score			
Baseline, n (%)	36 (100)	33 (100)	293
Baseline, mean (SD)	11.6 (6.9)	11.8 (7.0)	17.4 (6.6)
Adjusted LS mean change from baseline at last study visit (SE)	–1.8 (1.3)	1.3 (1.3)	–4.4 (6.5) *P* < 0.001[b]
Adjusted LS mean difference in change from baseline versus comparator (95% CI)	–3.0 (–5.3 to –0.8), *P* = 0.0086		NA
UPDRS Part III Score			
Baseline, n (%)	36 (100)	33 (100)	291
Baseline, mean (SD)	18.1 (9.9)	22.5 (11.7)	28.8 (13.7)
Adjusted LS mean change from baseline at last study visit (SE)	–1.5 (2.4)	–2.9 (2.4)	NR

End Point	Study 001/002 (FAS)		Study 004
	LCIG + PBO IR OLC Capsules N = 36	PBO LCIG + IR OLC Capsules N = 33	LCIG N = 354
Adjusted LS mean difference in change from baseline versus comparator (95% CI)	1.4 (–2.8 to 5.6), *P* = 0.5020		NA
UPDRS Part IV Score[a]			
Baseline, n (%)	36 (100)	33 (100)	292
Baseline, mean (SD)	7.9 (2.2)	7.9 (3.0)	NR
Adjusted LS mean change from baseline at last study visit (SE)	–1.1 (0.7)	0.1 (0.7)	NR
Adjusted LS mean difference in change from baseline versus comparator (95% CI)	–1.2 (–2.4 to –0.1), *P* = 0.0361		NA
UPDRS Part IV Score (Questions 32, 33, and 34)[a]			
Baseline, n (%)	36 (100)	33 (100)	NR
Baseline, mean (SD)	2.4 (1.6)	2.5 (2.0)	3.7 (2.4)
Adjusted LS mean change from baseline at last study visit (SE)	0.4 (0.5)	0.8 (0.5)	NR
Adjusted LS mean difference in change from baseline versus comparator (95% CI)	–0.4 (–1.1 to 0.4), *P* = 0.3578		NA

ANCOVA -= analysis of covariance; CI = confidence interval; FAS = full analysis set; IR = immediate-release; LCIG = levodopa/carbidopa intestinal gel; LS = least squares; NA = not applicable; NR = not reported; OLC = oral levodopa/carbidopa; PBO = placebo; SD = standard deviation; SE = standard error; UPDRS = Unified Parkinson's Disease Rating Scale.

Note: Each question is measured on a 5-point scale (0 to 4) where higher scores are associated with more disability.

The Part I score is the sum of the answers to the four questions that comprise Part I. The Part I score ranges from 0 to 16.

The Part II score is the sum of the answers to the 13 questions that comprise Part II. The Part II score ranges from 0 to 52.

The Part III score is the sum of the 27 answers provided to the 14 Part III questions. The Part III score ranges from 0 to 108.

The Part IV score is the sum of the answers provided to the 11 Part III questions. The Part IV score ranges from 0 to 44.

Questions 32, 33, and 34 on UPDRS Part IV are totalled to evaluate dyskinesias. The Part IV dyskinesia score ranges from 0 to 12.

The UPDRS total score is the sum of all questions included in Parts I to III of the UPDRS. The total score ranges from 0 to 176.

Treatment comparisons are based on an ANCOVA model including effects for treatment, country, and with the corresponding baseline as a covariate.

[a] Individual parts of the UPDRS were not part of the statistical testing hierarchy.

[b] Unadjusted mean change from baseline at last study visit. SD instead of SE. End point not corrected for multiple statistical testing.

Source: Study 001/002 Clinical Study Report,[26] Olanow et al. (2014),[27] Fernandez et al. (2015).[28]

EuroQol 5-Dimensions 3-Levels Questionnaire

Double-Blind, Randomized Controlled Trial

The EQ-5D-3L summary index score was also evaluated as a secondary outcome in Study 001/002. The adjusted LSMD in change from baseline was 0.07 (95% CI, –0.01 to 0.15; *P* = 0.0670). The EQ VAS (not adjusted for multiple statistical testing) was also evaluated and the adjusted LSMD in change from baseline was 11.4 (95% CI, 4.0 to 18.9; *P* = 0.0033). Details regarding the EQ-5D-3L in Study 001/002 are provided in Table 19.

Open-Label, Non-Comparative Study (Study 004)

Overall, the EQ-5D-3L summary index score increased from baseline to the last study visit (0.064 [SD 0.203]; *P* < 0.001). The EQ VAS also increased from baseline to the last study visit (14.0 [SD 24.8]; *P* < 0.001). Details pertaining to the change in EQ-5D during

Study 004 are presented in Table 19. The EQ-5D end points in Study 004 were not corrected for multiple statistical testing.

Table 19: Summary of EuroQol 5-Dimensions 3-Levels Questionnaire

End Point	Study 001/002 (FAS)		Study 004
	LCIG + PBO IR OLC Capsules N = 36	PBO LCIG + IR OLC Capsules N = 33	LCIG N = 354
EQ-5D-3L Summary Index Score[a]			
Baseline, n (%)	36 (100)	33 (100)	318
Baseline, mean (SD)	0.692 (0.151)	0.617 (0.181)	0.588 (0.195)
Adjusted LS mean change from baseline at week 12 (SE)	0.05 (0.04)	–0.02 (0.04)	0.064 (0.203), $P < 0.001$[c]
Adjusted LS mean difference in change from baseline versus comparator (95% CI)	0.07 (–0.01 to 0.15), $P = 0.0670$		NA
EQ VAS[b]			
Baseline, n (%)	36 (100)	32 (97)	318
Baseline, mean (SD)	63.9 (14.6)	57.0 (18.8)	50.2 (21.0)
Adjusted LS mean change from baseline at week 12 (SE)	5.2 (4.3)	–6.3 (4.3)	14.0 (24.8), $P < 0.001$[c]
Adjusted LS mean difference in change from baseline versus comparator (95% CI)	11.4 (4.0 to 18.9), $P = 0.0033$		NA

ANCOVA = analysis of covariance; CI = confidence interval; EQ-5D-3L = EuroQol 5-Dimensions 3-Levels questionnaire; EQ VAS = EuroQol visual analogue scale; FAS = full analysis set; IR = immediate-release; LCIG = levodopa/carbidopa intestinal gel; LS = least squares; NA = not applicable; NR = not reported; OLC = oral levodopa/carbidopa; PBO = placebo; QoL = quality of life; SD = standard deviation; SE = standard error; UPDRS = Unified Parkinson's Disease Rating Scale; VAS = visual analogue scale.

Note: EQ-5D-3L health states, defined by the EQ-5D-3l descriptive system, are converted into a single summary index by applying a formula that essentially attaches values (also called QoL weights or QoL utilities) to each of the levels in each dimension.

The EQ VAS records the patient's self-rated health on a scale from 0 to 100, where 100 is the "best imaginable health state" and 0 is the "worst imaginable health state."

Treatment comparisons are based on an ANCOVA model including effects for treatment and country and using the corresponding baseline as a covariate.

[a] The end point in the statistical testing hierarchy failed prior to the evaluation of this end point.

[b] Individual parts of the UPDRS were not part of the statistical testing hierarchy.

[c] Unadjusted mean change from baseline at last study visit. SD instead of SE. End point not corrected for multiple statistical testing.

Source: Study 001/002 Clinical Study Report,[26] Olanow et al. (2014),[27] Fernandez et al. (2015).[28]

Zarit Burden Interview

Double-Blind, Randomized Controlled Trial

The ZBI total score was also evaluated as a secondary outcome in Study 001/002. The adjusted LSMD in change from baseline was –4.5 (95% CI, –10.7 to 1.7; $P = 0.1501$). Details regarding the ZBI in Study 001/002 are provided in Table 20.

Open-Label, Non-Comparative Study (Study 004)

No details with regards to the ZBI were provided in Study 004.

Table 20: Summary of Zarit Burden Interviews

End Point	Study 001/002 (FAS)		Study 004
	LCIG + PBO IR OLC Capsules N = 36	PBO LCIG + IR OLC Capsules N = 33	LCIG N = 354
ZBI Total Score[a]			
Baseline, n (%)	23 (64)	23 (70)	NR
Baseline, mean (SD)	23.9 (11.6)	23.0 (13.9)	NR
Adjusted LS mean change from baseline at week 12 (SE)	–2.8 (3.7)	1.7 (3.3)	NR
Adjusted LS mean difference in change from baseline versus comparator (95% CI)	–4.5 (–10.7 to 1.7), *P* = 0.1501		NA

ANCOVA = analysis of covariance; CI = confidence interval; FAS = full analysis set; IR = immediate-release; LCIG = levodopa/carbidopa intestinal gel; LS = least squares; NA = not applicable; NR = not reported; OLC = oral levodopa/carbidopa; PBO = placebo; SD = standard deviation; SE = standard error; ZBI = Zarit Burden Interview.

Note: The ZBI is a 22-item questionnaire regarding the caregiver–patient relationship and evaluates the caregiver's health condition, psychological well-being, finances, and social life. Each question is answered on a 5-point scale where 0 = never, 1 = rarely, 2 = sometimes, 3 = quite frequently, and 4 = nearly always. The caregiver burden is evaluated by the total score (range: 0 to 88) obtained from the sum of the answers to the 22 questions. Higher scores are associated with a higher level of burden for the caregiver.

Treatment comparisons are based on an ANCOVA model including effects for treatment, country, and with the corresponding baseline as a covariate.

[a] The end point in the statistical testing hierarchy failed prior to the evaluation of this end point.

Source: Study 001/002 Clinical Study Report,[26] Olanow et al. (2014),[27] Fernandez et al. (2015).[28]

Harms

Only those harms identified in the review protocol are reported in Table 4. Detailed harms data are presented in Table 21.

Double-Blind, Randomized Controlled Trial

Adverse Events

Overall, 95% and 100% of patients experienced AEs in the LCIG + PBO IR OLC capsules group and the PBO LCIG + IR OLC capsules group, respectively. The frequencies of AEs were relatively similar across treatment groups. The most common AEs were fall (11% versus 12%), atelectasis (8% versus 0%), anxiety (8% versus 3%), confusional state (8% versus 3%), oedema peripheral (8% versus 0%), oropharyngeal pain (8% versus 0%), and upper respiratory tract infection (8% versus 0%) in the LCIG + PBO IR OLC capsules and PBO LCIG + IR OLC capsules groups, respectively.

Serious Adverse Events

Fewer patients experienced SAEs in the LCIG + PBO IR OLC capsules group compared with the PBO LCIG + IR OLC capsules group (14% versus 21%, respectively). The most common SAEs were confusional state (5% versus 0%) and pneumonia (0% versus 6%) in the LCIG + PBO IR OLC capsules and PBO LCIG + IR OLC capsules groups, respectively.

Withdrawals Due to Adverse Events

Overall, one patient (3%) and two patients (6%) withdrew due to AEs in the LCIG + PBO IR OLC capsules and PBO LCIG + IR OLC capsules groups, respectively. The most common reasons were hallucination (3% versus 0%), psychotic disorder (3% versus 0%), peritonitis

(0% versus 3%), post-procedural complication (0% versus 3%), and post-procedural discharge (0% versus 3%) in the LCIG + PBO IR OLC capsules and PBO LCIG + IR OLC capsules groups, respectively.

Mortality

No deaths were reported in Study 001/002.

Notable Harms

Most patients experienced device-related complications across both treatment groups (92% and 85% in the LCIG + PBO IR OLC capsules group and PBO LCIG + IR OLC capsules group, respectively).

Overall, 76% compared with 79% of patients and 57% compared with 56% of patients experienced long-term complications of PEG-J and risks of PEG-J insertion in the LCIG + PBO IR OLC capsules group and the PBO LCIG + IR OLC capsules group, respectively. The most common long-term complications of PEG-J were complication of device insertion (57% versus 44%), procedural pain (30% versus 35%), and incision-site erythema (19% versus 12%), while the most common risks of PEG-J insertion were abdominal pain (51% versus 32%) and pneumoperitoneum (11% versus 3%) in the LCIG + PBO IR OLC capsules and PBO LCIG + IR OLC capsules groups, respectively.

In general, a similar number of patients (70% compared with 71%) experienced GI AEs, the most common being nausea (30% versus 21%), constipation (22% versus 21%), and flatulence (16% versus 12%) in the LCIG + PBO IR OLC capsules and PBO LCIG + IR OLC capsules groups, respectively.

More patients experienced psychiatric disorders in the LCIG + PBO IR OLC capsules group compared with the PBO LCIG + IR OLC capsules group (46% compared with 29%). The most common were depression (11% versus 3%), insomnia (11% versus 12%), anxiety (8% versus 3%), and confusional state (8% versus 3%) in the LCIG + PBO IR OLC capsules and PBO LCIG + IR OLC capsules groups, respectively.

A total of 3% and 9% of patients experienced polyneuropathy and associated signs and symptoms, the most common reason being balance disorder (3% compared with 6%) in the LCIG + PBO IR OLC capsules and PBO LCIG + IR OLC capsules groups, respectively.

Fewer patients experienced nervous system disorders in the LCIG + PBO IR OLC capsules group compared with the PBO LCIG + IR OLC capsules group (30% compared with 47%). The most common were dyskinesia (14% versus 12%), dizziness (8% versus 6%), and headache (8% versus 12%) in the LCIG + PBO IR OLC capsules and PBO LCIG + IR OLC capsules groups, respectively.

In general, a similar number of patients (22% compared with 27%) experienced vascular disorders, the most common being orthostatic hypotension (14% versus 24%) and hypertension (8% versus 0%) in the LCIG + PBO IR OLC capsules and PBO LCIG + IR OLC capsules groups, respectively.

Open-Label, Non-Comparative Study (Study 004)

Nearly all (92%) patients experienced at least one AE. The most frequently reported AEs were nausea, fall (15%), constipation (15%), insomnia (14%), and urinary tract infection (11%). SAEs were reported in 32% of patients, the most common reasons being

complication of device insertion (7%), abdominal pain (3%), peritonitis (3%), polyneuropathy (3%), PD (3%), pneumoperitoneum (3%), hip fracture (2%), pneumonia (2%), device dislocation (2%), and depression (1%).

Overall, 27 patients discontinued the trial due to AEs. Five patients (2%) withdrew during the NJ period and 22 patients (7%) withdrew during the PEG-J period. The most common reasons for discontinuation were complications of device insertion (2%) and procedure- or device-related AEs (2%).

A total of eight deaths occurred during Study 004; however, none were considered by the investigators to be related to the study drug.

The majority of patients (87%) experienced device-related complications, most of which were intestinal tube-related (51%). Furthermore, the majority (69%) also experienced procedure- and/or device-related AEs. The most frequently reported notable harms were complication of device insertion (34%), abdominal pain (27%), procedural pain (20%), excessive granulation tissue (15%), post-operative wound infection (15%), incision-site erythema (13%), procedural-site reaction (9%), post-procedural discharge (8%), incision-site pain (6%), and pneumoperitoneum (6%). Aspiration-related AEs occurred in 15% of patients and polyneuropathy-related AEs occurred in 7% of patients.

Table 21: Harms

Harms	Study 001/002 (Safety Set)		Study 004
	LCIG + PBO IR OLC Capsules N = 37	PBO LCIG + IR OLC Capsules N = 34	LCIG N = 324
AEs			
Patients with > 0 AEs, n (%)	35 (95)	34 (100)	298 (92)
Most Common AEs[a]			
Fall	4 (11)	4 (12)	49 (15)
Atelectasis	3 (8)	0	NR (2)
Anxiety	3 (8)	1 (3)	NR
Confusional state	3 (8)	1 (3)	NR
Oedema peripheral	3 (8)	0	NR
Oropharyngeal pain	3 (8)	0	NR
Upper respiratory tract infection	3 (8)	0	NR
Pyrexia	2 (5)	0	NR (2)
Pneumonia	1 (3)	2 (6)	NR (3)
Urinary tract infection	0	4 (12)	37 (11)
SAEs			
Patients with > 0 SAEs, n (%)	5 (14)	7 (21)	105 (32)
Most Common SAEs[b]			
Confusional state	2 (5)	0	NR
Pneumonia	0	2 (6)	6 (2)
Complication of device insertion	1 (3)	1 (3)	21 (7)
WDAEs			

Harms	Study 001/002 (Safety Set)		Study 004
	LCIG + PBO IR OLC Capsules N = 37	PBO LCIG + IR OLC Capsules N = 34	LCIG N = 324
WDAEs, n (%)	1 (3)	2 (6)	27 (8)
Most Common Reasons			
Procedure- or device-related AEs	NR	NR	8 (2)
Complication of device insertion	NR	NR	6 (2)
Abdominal pain	NR	NR	3 (1)
Dyskinesia	NR	NR	2 (1)
Death of unknown etiology	NR	NR	2 (1)
Suicide	NR	NR	2 (1)
Vomiting	NR	NR	1 (< 1)
QT prolongation	NR	NR	1 (< 1)
Anxiety	NR	NR	1 (< 1)
Pneumonia	NR	NR	1 (< 1)
Hallucination	1 (3)	0	1 (< 1)
Psychotic disorder	1 (3)	0	NR
Peritonitis	0	1 (3)	NR
Post-procedural complication	0	1 (3)	NR
Post-procedural discharge	0	1 (3)	NR
Deaths			
Number of deaths, n (%)	0	0	8 (2)
Notable Harms, n (%)			
Device-related complications	**34 (92)**	**29 (85)**	**NR (87)**
Stoma complication	15 (41)	15 (44)	NR
Intestinal tube complication	14 (38)	12 (35)	NR (51)
PEG-J complication	11 (30)	12 (35)	NR (35)
Pump complication	5 (14)	8 (24)	NR
Pump or stoma complication	NR	NR	NR (36)
Other[c]	17 (46)	13 (38)	
Procedure and Device-Associated AEs			
Long-term complications of PEG-J	**28 (76)**	**27 (79)**	**NR (69)**
Complication of device insertion	21 (57)	15 (44)	113 (34)
Procedural pain	11 (30)	12 (35)	67 (20)
Incision-site erythema	7 (19)	4 (12)	42 (13)
Post-procedural discharge	4 (11)	3 (9)	NR (8)
Post-operative wound infection	4 (11)	8 (24)	50 (15)
Excessive granulation tissue	2 (5)	0	52 (15)
Procedural-site reaction	2 (5)	2 (6)	NR (9)
Incision-site cellulitis	1 (3)	1 (3)	NR
Medical device site reaction	1 (3)	0	NR
Incision-site complication	0	1 (3)	NR

Harms	Study 001/002 (Safety Set)		Study 004
	LCIG + PBO IR OLC Capsules N = 37	PBO LCIG + IR OLC Capsules N = 34	LCIG N = 324
Post-procedural complication	0	1 (3)	NR
Post-procedural constipation	0	1 (3)	NR
Post-procedural discomfort	0	1 (3)	NR
Post-procedural hemorrhage	0	1 (3)	NR
Post-procedural infection	0	1 (3)	NR
Procedural nausea	0	1 (3)	NR
Incision-site pain	NR	NR	NR (6)
Risk of PEG-J insertion	**21 (57)**	**19 (56)**	**NR**
Abdominal pain	19 (51)	11 (32)	101 (31)
Pneumoperitoneum	4 (11)	1 (3)	NR (6)
Post-operative ileus	2 (5)	0	NR
Abdominal discomfort	1 (3)	3 (9)	NR
Abdominal pain upper	1 (3)	2 (6)	NR
Peritonitis	0	1 (3)	9 (3)
GI AEs	**26 (70)**	**24 (71)**	NR
Nausea	11 (30)	7 (21)	54 (17)
Constipation	8 (22)	7 (21)	47 (15)
Flatulence	6 (16)	4 (12)	NR
Hiatus hernia	3 (8)	2 (6)	NR
Abdominal distension	2 (5)	1 (3)	NR
Diarrhea	2 (5)	1 (3)	NR
Dyspepsia	2 (5)	1 (3)	NR
Vomiting	2 (5)	4 (12)	NR
Gastritis	1 (3)	3 (9)	NR
Mouth ulceration	1 (3)	0	NR
Gastroesophageal reflux disease	0	1 (3)	NR (2)
Peritonitis	0	1 (3)	NR
Reflux oesophagitis	0	2 (6)	NR
Psychiatric disorders	**17 (46)**	**10 (29)**	NR
Depression	4 (11)	1 (3)	NR
Insomnia	4 (11)	4 (12)	44 (14)
Anxiety	3 (8)	1 (3)	NR (1)
Confusional state	3 (8)	1 (3)	NR
Hallucination	2 (5)	1 (3)	NR
Psychotic disorder	2 (5)	1 (3)	NR
Sleep disorder	2 (5)	0	NR
Delusion	1 (3)	0	NR
Mental status changes	0	1 (3)	NR
Shared psychotic disorder	0	1 (3)	NR

Harms	Study 001/002 (Safety Set)		Study 004
	LCIG + PBO IR OLC Capsules N = 37	PBO LCIG + IR OLC Capsules N = 34	LCIG N = 324
Sleep attacks	0	1 (3)	NR
Polyneuropathy and associated signs and symptoms	**1 (3)**	**3 (9)**	NR (7)
Balance disorder	1 (3)	2 (6)	NR
Asthenia	1 (3)	1 (3)	NR
Hypoesthesia	1 (3)	0	NR
Paresthesia	1 (3)	0	NR
Neuropathy peripheral	0	1 (3)	NR (1)
Speech disorder	0	1 (3)	NR
Nervous system disorders	**11 (30)**	**16 (47)**	NR
Dyskinesia	5 (14)	4 (12)	NR
Dizziness	3 (8)	2 (6)	NR
Headache	3 (8)	4 (12)	NR
Dizziness postural	1 (3)	1 (3)	NR
Freezing phenomenon	1 (3)	2 (6)	NR
Parkinson disease	1 (3)	2 (6)	NR
Neuropathy peripheral	0	1 (3)	NR (1)
Tremor	0	1 (3)	NR
Vascular disorders	**8 (22)**	**9 (27)**	NR
Orthostatic hypotension	5 (14)	8 (24)	NR
Hypertension	3 (8)	0	NR

AE = adverse event; GI = gastrointestinal; IR = immediate-release; LCIG = levodopa/carbidopa intestinal gel; OLC = oral levodopa/carbidopa; NR = not reported; PBO = placebo; PEG- J = percutaneous endoscopic gastrostomy with jejunal extension; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] Frequency > 5%.

[b] Frequency ≥ 5%.

[c] Events that could not clearly be assigned to another specified category based on investigator judgment.

Source: Study 001/002 Clinical Study Report,[26] Olanow et al. (2014),[27] Fernandez et al. (2015).[28]

Discussion

Summary of Available Evidence

The CDR review of LCIG in 2009 included two trials: the DIREQT and NPP-001-99 studies, both open-label RCTs.[69,70] Based on the evidence reviewed by CDR, CEDAC recommended that LCIG "not be listed" based on cost considerations and quality issues in the two trials reviewed (i.e., the open-label designs, high proportions of withdrawals in trials of small sample size, and patient populations that were not representative of those most likely to use Duodopa). The current CDR review was undertaken in response to a drug plan resubmission that requested that the evidence for the use of LCIG in patients with PD be reviewed again in light of the availability of "new evidence." Therefore, for the current review, only new clinical evidence that has become available since the 2009 CDR review was considered for inclusion in the CDR systematic review.

New Evidence Identified in the Current Review

A total of 20 trials met the inclusion criteria of the CDR systematic review.

Double-Blind, Randomized Controlled Trial

Study 001/002 (N = 71) was a DB, double-dummy, active-controlled, multi-centre, multinational, phase III superiority RCT that recruited patients from North America (excluding Canada). The study objective was to evaluate the efficacy and safety of LCIG for the treatment of patients with advanced levodopa-responsive Parkinson disease who do not have satisfactory control of severe, debilitating motor fluctuations and hyper-/dyskinesia despite optimized treatment with available combinations of PD medicinal products and for whom the benefits of this treatment may outweigh the risks associated with the insertion and long-term use of the PEG-J tube required for administration. Patients were randomized to a 1:1 ratio of optimally titrated LCIG (20 mg/mL levodopa and

5 mg/mL carbidopa monohydrate solution) in addition to placebo IR OLC capsules or optimally titrated IR OLC 100 mg/25 mg capsules in addition to placebo LCIG. The primary efficacy outcome was change from baseline at final visit (week 12) in the mean number of "off" hours recorded in the PDHD during the three consecutive days prior to study visit, normalized to a 16-hour waking day. The predefined key secondary outcome was change from baseline to final visit (week 12) in the mean number of normalized "on" hours without troublesome dyskinesia (defined as a composite of "on" time without dyskinesia and "on" time with non-troublesome dyskinesia). Other secondary outcomes included change from baseline in the PDQ-39 summary index score, CGI-I score, UPDRS Part II ADL subscore, UPDRS Part III motor subscore, EQ-5D-3L summary index score, and ZBI score. Although Study 001/002 had some methodological limitations, no major limitations were identified. Limitations of the trial included differences in PD severity between groups at baseline and the potential for unblinding due to non-compliance with active IR OLC capsules in the comparator group.

Overall, Study 001/002 addresses the majority of limitations identified with the previous trials included in the 2009 CDR review. Study 001/002 uses treatment allocation concealment methods to blind patients (as opposed to the previous open-label trials) and administers LCIG as would be done in clinical practice (i.e., through a PEG-J tube instead of NJ tube). Furthermore, there were also few withdrawals during the 12-week follow-up. The clinical experts consulted by CDR for this review also highlighted that Study 001/002

appears to have recruited patients with characteristics similar to those with advanced PD who would be considered eligible for treatment with LCIG.

Open-Label, Non-Comparative Study (Study 004)

Study 004 (N = 354) was a non-comparative, multinational, multi-centre, open-label, long-term safety study that recruited patients from North America (including Canada) and western Europe. Patients included in this study were not previously treated with LCIG in Study 001/002. The study objective was to evaluate the safety of LCIG for the treatment of patients with advanced levodopa-responsive PD over a 54-week period. LCIG was delivered as an aqueous solution containing 20 mg/mL levodopa and 5 mg/mL carbidopa monohydrate packaged in 100 mL cassettes administered as a morning bolus dose followed by continuous infusion at a constant rate for the remainder of each patient's waking day (approximately 16 hours) with additional rescue doses during the day, if clinically indicated. The primary objective was to evaluate the long-term safety of LCIG based on AEs, device complications, and number of completers. All AEs were considered as TEAEs, defined as those that began or worsened from the time of NJ tube insertion until 30 days after PEG-J removal. Long-term efficacy (as measured by "off" time, "on" time with and without troublesome dyskinesia, and UPDRS) and QoL (as measured by PDQ-39, EQ-5D-3L, EQ VAS, and CGI-I) were evaluated as secondary end points. Key limitations of Study 004 include its open-label and non-comparative study design as well as the lack of adjustments for multiple statistical testing.

Additional Non-Comparative, Open-Label Studies

Patients who completed Study 001/002 had the option to enrol in an optional 12-month open-label safety extension study (Study 003, N = 62). Furthermore, patients who completed either Study 003 or Study 004 were able to enrol in Study 005 (N = 262) for up to 6.9 years of follow-up.

A total of 16 other prospective, open-label, non-comparative trials were also identified in the CDR systematic review. [10-25] The sample sizes of these trials ranged between nine and 375 enrolled patients; follow-ups ranged between four and 36 months. Treatment with LCIG was administered to all patients and change from baseline to last study visit was evaluated for relevant outcomes. Key limitations of these trials (including Study 003 and Study 005) include their open-label and non-comparative study design.

Interpretation of Results

Efficacy

Compared with the IR OLC group, the LCIG group had a statistically significant reduction in daily normalized "off" time at week 12 (the primary outcome) based on their Parkinson disease diary entries. Overall, "off" time was identified as being among the most important end points by the patient groups who provided input for this CDR submission. Sensitivity analyses of the primary end point using MMRM and those requested by the FDA considering different approaches (including and excluding certain covariates) to the primary ANCOVA analysis were also consistent with the primary analysis. The robustness of the treatment effect was also noted by the FDA.[53,67,68] Although not provided in the manufacturer's submission, the FDA conducted a worst-case analysis in which the data for the primary end point were imputed with the overall mean average baseline "off" time for the dropouts in the LCIG group, and with the overall mean average "off" time at week 12 for

those in the OLC group. Overall, the results were also consistent with those of the primary analysis (P = 0.0046).[53,67,68] Despite the robustness of the primary end point, the FDA also noted that a decrease in "off" time is a somewhat indirect outcome, given that it may not necessarily lead to desirable outcomes — for example, if the decrease in "off" time was replaced with an increase in "asleep" time or "on" time with troublesome dyskinesia.[53,67,68]

The evaluation of "off" time as the primary end point in Study 001/002 was supported by the evaluation of a key secondary end point (adjusted for multiple statistical testing): "on" time without troublesome dyskinesia (a composite of "on" time without dyskinesia and "on" time with non-troublesome dyskinesia). Improvement in functional "on" time is considered by the FDA as the most important end point for treating patients with motor fluctuations and is said to provide a better indication of improvement in patient functioning.[53,67,68] Furthermore, the patient input submitted for this review highlighted the importance of "on" time as a desirable outcome. Overall, the LCIG group also had a statistically significant improvement in daily normalized "on" time without troublesome dyskinesia at week 12. The results were primarily driven by the increase in "on" time without dyskinesia, whereas the change in "on" time with non-troublesome dyskinesia was not statistically significant. These results support the benefit in "on" time associated with LCIG treatment, especially because the results are being driven by the more desirable component ("on" time without dyskinesia). Although statistical analyses demonstrate that there is no statistically significant difference in "on" time with troublesome dyskinesia was reported between the two groups, it should be noted that Study 001/002 was not powered to detect a difference in this end point. Similar observations were also noted by the FDA.[53,67,68]

In general, the PDHD has been shown to demonstrate acceptable predictive validity in the assessment of the amount of "on" and "off" time that patients experience in a 24-hour period. All patients were trained in the completion of the diary by an instructional DVD and were required to demonstrate 75% completion and concordance with the investigators, leading to more consistent results. The PDHD has also demonstrated good reproducibility, test–retest reliability, and precision. One study conducted by Hauser et al. suggests that a one-hour reduction in "off" time was considered to be an MCID in actively treated patients.[61] Given that the benefit associated with LCIG treatment exceeds the reported MCID –1.00 hour, the improvement in "off" time reported in Study 001/002 is considered clinically meaningful. No MCID was identified for the change in "on" time.

Although the study protocol indicated that primary end point analyses would be performed for the subgroups of patients with PD for a duration of ≤ 10 years and ≥ 10 years, the results of these analyses were not provided in the manufacturer-submitted materials. An examination of the interaction of treatment by duration of PD was conducted by the FDA; the result suggested that the interaction was not statistically significant (P = 0.135).[53,67,68] However, Study 001/002 was not powered to detect a difference in the subgroups of patients with PD for a duration ≤ 10 years and ≥ 10 years.

Overall, randomization appeared to be successful; however, patients experienced less "off" time and less "on" time at baseline in the LCIG + PBO IR OLC capsules group, which may indicate less severe PD. Given that PD is a degenerative disease, patients with more severe PD may not benefit from treatment to the same extent as those with less severe disease. Limiting the benefit in the PBO LCIG + IR OLC capsules group could potentially result in overestimating the treatment effect associated with LCIG therapy. However, the clinical expert consulted for this CDR review suggested that any such bias is unlikely to explain the magnitude of the treatment effect. Furthermore, compliance with the active IR

OLC capsules in the PBO LCIG + IR OLC capsules group was 76%. Patients who were not compliant with the IR OLC capsules in this treatment group would not receive any PD therapies (i.e., only PBO LCIG). Given that the symptoms of PD are well known (i.e., "off" state symptoms, such as tremors or immobility) and that non-compliant patients may have experienced symptoms of uncontrolled PD, some patients may inadvertently have been unblinded to treatment status. Unblinding may lead to biases in the reporting of subjective outcomes (i.e., "on" and "off" states, HRQoL, and AEs).

Study 001/002 also evaluated aspects of health not captured under general health questionnaires that may be relevant to patients with PD using the PDQ-39 summary index score (adjusted for multiple statistical testing). Overall, the PDQ-39 has been validated and demonstrated to be comprehensive, feasible, responsive, and reliable, with good internal consistency and test–retest reliability. Findings from one study conducted by Peto et al. showed a mean MCID of –1.6 for the summary index score.[62] In Study 001/002, LCIG was associated with a statistically significant reduction in the summary index score compared with IR OLC. Given that the benefit associated with LCIG treatment exceeds the reported MCID (–1.6), the improvement in PDQ-39 summary index score is considered clinically meaningful. Overall, the results of the individual domains score were consistent with the summary index score. Although scores for the individual domains of the PDQ-39 were also provided, they were not adjusted for multiple statistical testing and should be considered hypothesis-generating.

The CGI-I was also evaluated in Study 001/002 and provided an overall assessment of the clinician's view of the patient's global functioning, which is used to compare before- and after-treatment changes. Patients treated with LCIG experienced a statistically significant reduction in the CGI-I scale compared with patients in the IR OLC group. Although the CGI-I was validated and demonstrated correlation with the Hoehn and Yahr stage, no information was found on the MCID; therefore, the clinically meaningfulness of the results remains unclear.

The UPDRS was also analyzed in Study 001/002. The UPDRS is a standard investigator rating tool for measuring parkinsonian signs and symptoms. Only parts II and III of the UPDRS were part of the testing hierarchy (adjusted for multiple statistical testing). Overall, the UPDRS has been validated and demonstrated to be feasible and reliable. Furthermore, Parts II and III specifically have shown good inter-rater reproducibility. Among available studies, the estimated MCID for the ADL component (Part II) and motor component (Part III) were –2.3 and –6.5 points in patients with advanced PD, respectively.[63] Compared with IR OLC capsules, LCIG was associated with a statistically significant reduction in the UPDRS Part II score. Given that the benefit associated with LCIG treatment exceeds the reported MCID (–3.0 and –2.3, respectively), the improvement in the UPDRS Part II is considered clinically meaningful. Conversely, no statistically significant difference in the UPDRS Part III score was reported between the two treatment groups. Study 001/002 also evaluated other components of the UPDRS (Part I, Part IV, Part I, II, and II summary score as well as questions 32, 33, and 34 only in Part IV). Given that these end points were not adjusted for multiple statistical testing, no statistical interpretation should be made; therefore, the clinical importance of these changes remains unclear.

Study 001/002 also evaluated HRQoL using the EQ-5D-3L and caregiver burden using the ZBI. The adjusted LSMD from baseline to week 12 in both the EQ-5D-3L summary index score and the ZBI total score were not statistically significant across treatment groups. The results for the EQ VAS should be considered exploratory; the clinical importance of these

changes remains unclear given that this end point was not considered in the statistical testing hierarchy.

Overall, Study 001/002 was relatively short in duration (12 weeks) considering that PD therapies would be expected to continue for a patient's lifetime. However, patients enrolled in Study 001/002 were provided the opportunity to continue treatment in a 12-month, open-label safety extension study (Study 003) that provided longer-term safety and efficacy associated with LCIG therapy. Study 003 (summarized in Appendix 6) began immediately after Study 001/002. All patients (N = 62) were hospitalized and re-titrated to the optimum LCIG dose for two to seven days, after which they continued on open-label LCIG infusion for the remainder of the 52 weeks. The LCIG intervention was administered in a similar manner as Study 001/002 — i.e., continuous infusion during the day (for approximately 16 hours) and cessation at night, when all patients were permitted to take rescue IR OLC if medically indicated. The primary objective was to evaluate the long-term safety of LCIG based on the frequency and severity of AEs; however, efficacy and QoL were also evaluated as secondary end points. In general, LCIG-naive patients (i.e., those treated with active IR OLC capsules in Study 001/002) experienced a significant reduction in daily normalized "off" time at week 52 compared with their baselines, while LCIG-experienced patients (i.e., those treated with active LCIG in Study 001/002) continued to experience reduced daily normalized "off" time at week 52. The change from baseline to week 52 in "on" time without troublesome dyskinesia (a composite of "on" time without dyskinesia and "on" time with non-troublesome dyskinesia) was also evaluated in Study 003. In general, improvement was reported in both LCIG-naive patients and LCIG-experienced patients in daily normalized "on" time without troublesome dyskinesia at week 52. Although the efficacy results of Study 003 were consistent with the results observed in Study 001/002, it is important to note the limitations, which include uncontrolled open-label study design and the fact that the trial enrolled patients who were deemed likely to benefit from LCIG.

Longer-term safety and efficacy associated with LCIG therapy were also evaluated in Study 004 (54-week follow-up) which included a much larger sample of patients (N = 354) compared with Study 003. The LCIG intervention was administered in a manner similar to Study 001/002 — i.e., continuous infusion during the day (approximately 16 hours) and cessation at night, when all patients were permitted to take IR OLC if medically indicated. In general, patients experienced a significant reduction in daily normalized "off" time at week 54 compared with their baselines. The change from baseline to week 54 in "on" time without troublesome dyskinesia (a composite of "on" time without dyskinesia and "on" time with non-troublesome dyskinesia) was also evaluated in Study 004. In general, improvement was also reported in daily normalized "on" time without troublesome dyskinesia at week 54.

Patients who completed either Study 003 or Study 004 were eligible to enroll into Study 005 (N = 262), a prospective, open-label, non-comparative trial that evaluated the safety and efficacy of LCIG with up to 6.9 years of follow-up. The LCIG intervention was administered in a manner similar to that of Study 001/002 — i.e., continuous infusion during the day (approximately 16 hours) and cessation at night, when all patients were permitted to take IR OLC if medically indicated. The primary objective was to evaluate the long-term safety; however, efficacy and QoL were also evaluated as secondary end points. Overall, efficacy and safety were consistent with the results observed in Study 001/002; however, as with Study 003, it is important to note the limitations, which include uncontrolled open-label study design and the fact that the trial enrolled patients who were deemed likely to benefit from LCIG.

A total of 16 other prospective, open-label, non-comparative trials were also identified in the CDR systematic review.[10-25] The efficacy results of the open-label trials were similar to the results observed in Study 001/002; however, the limitations were similar to those of Study 001/002.

Harms

Given that LCIG is administered through a PEG-J tube, harms that should be considered include complications related to the device (e.g., its pump and tubes), the administration of LCIG, and the procedures required for the initial insertion, possible replacement, or repositioning of the PEG-J tube.[53,67,68]

A similar proportion of patients experienced AEs across both treatment groups. The most common AEs were fall, atelectasis, anxiety, confusional state, oedema peripheral, oropharyngeal pain, and upper respiratory tract infection. More patients experienced SAEs in the PBO LCIG + IR OLC capsules group compared with the LCIG + PBO IR OLC capsules group. The most common SAEs were confusional state and pneumonia. Overall, few patients withdrew due to AEs in both groups. The most common reasons were hallucinations, psychotic disorder, peritonitis, post-procedural complication, and post-procedural discharge. No deaths were reported in Study 001/002.

Most patients experienced device-related complications in both treatment groups. Overall, a similar proportion of patients experienced long-term complications of PEG-J and risks related to PEG-J insertion. The most common long-term complications of PEG-J were complication of device insertion, procedural pain, and incision-site erythema, while the most common risks of PEG-J insertion were abdominal and pneumoperitoneum. In general, a similar number of patients also experienced GI AEs, the most common being nausea, constipation, and flatulence. More patients experienced psychiatric disorders in the LCIG + PBO IR OLC capsules group compared with the PBO LCIG + IR OLC capsules group. The most common were depression, insomnia, anxiety, and confusional state, which are typically associated with levodopa. A minority of patients experienced polyneuropathy and associated signs and symptoms, the most common reason being balance disorder. Fewer patients experienced nervous system disorders in the LCIG + PBO IR OLC capsules group compared with the PBO LCIG + IR OLC capsules group. The most common were dyskinesia, dizziness, and headache. In general, a similar number of patients experienced vascular disorders, the most common being orthostatic hypotension and hypertension.

Device insertion, abdominal pain, pneumoperitoneum, nausea, and depression were notable AEs that occurred more frequently in the LCIG + PBO IR OLC capsules group compared with the PBO LCIG + IR OLC capsules group, while post-operative wound infection, vomiting, and orthostatic hypotension occurred more frequently in the PBO LCIG + IR OLC capsules group. However, given the small sample size of Study 001/002, it is difficult to make any definitive conclusions in regard to safety.

Generally, serious and non-serious AEs reported in Study 001/002 were consistent with the known AE profile of levodopa/carbidopa (e.g., depression, anxiety, confusion) and of PD patients who have undergone the PEG-J procedure. Further, the comparator group in Study 001/002 included levodopa/carbidopa as a treatment; thus, between-treatment differences in AE related to levodopa/carbidopa were not expected. It is theoretically possible that continuous infusion may result in a reduced frequency of total or specific drug-related AEs by minimizing peaks and troughs in levodopa plasma levels in the same way motor

complications of levodopa may be reduced.[71] However, the included trials are likely too small to detect many potential differences.

The primary objective of Study 003 was to evaluate the long-term safety of LCIG based on the frequency and severity of AEs after 12 months of treatment. Similar to Study 001/002, most patients experienced AEs that were consistent with the safety profiles of levodopa/carbidopa and the PEG-J procedures. Overall, no new safety signals were identified after one year of treatment. Safety results reported in Study 004 and in Study 005 also highlighted that most patients experienced AEs that were consistent with the safety profiles of levodopa/carbidopa and the PEG-J procedures, with no new safety signals following up to five years of treatment. A total of 16 other prospective, open-label, non-comparative trials were also identified in the CDR systematic review and were supportive of the results from Study 004 and Study 005.[10-25]

Other Considerations

The Health Canada–approved product monograph indicates that the PEG-J tube required for the administration of LCIG will likely require periodic replacement (emergency tube replacement as well as routine standard of care).[9] The Health Canada–approved product monograph indicates that a total of 14% of patients required at least one PEG tube replacement and 43% of patients required one J-tube replacement.[9] Approximately half of the patients who had at least one J-tube replacement also required a subsequent J-tube replacement.[9]

Patients who undergo the PEG-J procedure require antibiotic prophylaxis given that they are potentially at risk for post-operative peristomal infections. The Health Canada–approved product monograph indicates that a total of 21% of patients had post-operative AEs related to wound infection.[9] Antibiotic prophylaxis has been shown to markedly reduce the risk of peristomal infection; therefore, it is recommended for all patients undergoing PEG-J placement.[9]

Currently the only available treatment option for patients with more advanced PD is DBS, a surgery in which a high-frequency current is delivered through electrodes inserted deep into the brain. The 2009 CDR review noted that DBS is likely the most relevant comparator, given that both LCIG and DBS will likely be indicated for similar patient populations and that access to both treatments would also likely be similar (i.e., not available in all centres). However, no trials comparing LCIG and DBS were identified in either the previous (2009) or current CDR systematic review.

Potential Place in Therapy[2]

Since its introduction into clinical practice almost 50 years ago, levodopa remains the most effective treatment for the motor manifestations of PD. However, levodopa is only a symptomatic treatment. It does not slow the underlying neurodegenerative process of PD; the number of functioning nigrostriatal pathway neurons continues to decline. As the number of remaining functioning nigrostriatal neurons falls, the midbrain's ability to convert levodopa to dopamine — and thereby stimulate the striatum — becomes increasingly impaired. Clinically, this decline in the nigrostriatal neuron population is experienced by patients as a gradual transition from the initial months or years in which levodopa produces a sustained, continuous improvement in motor function to a state in which individual doses

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

of levodopa produce increasingly shorter periods of improvement that wear off quickly. As PD advances, the patient increasingly alternates between “on” periods, when they are mobile, and “off” periods, when they are immobile. Generally, the fluctuation between the “on” and “off” states can be related to when individual doses of levodopa are administered. To some extent, these fluctuations can be minimized by spacing levodopa doses closer together and using additional drugs, such as sustained-release levodopa preparations, drugs that inhibit the metabolism of levodopa, or direct dopamine agonists (the latter generally have a longer duration of action than levodopa, but are also generally less effective). For relatively rapid relief of fluctuations, particularly those that occur unpredictably, injectable apomorphine is another option. Although patients can learn to adapt to these fluctuations to some extent, the fluctuations can be unpredictable, severe, and have a major impact on their ability to carry out ADL.

A key limitation of oral pharmacological strategies for managing “on” and “off” fluctuations is the suboptimal absorption of the drugs from the GI tract. This is particularly problematic for levodopa, which must compete with other small amino acids to gain access to the same small-amino-acid transporter in the gastric mucosa in order to pass from the lumen of the stomach into the bloodstream. LCIG alleviates this problem because levodopa is delivered directly to the jejunum through a jejunostomy tube. In addition to improving the reliability of levodopa absorption, the jejunostomy tube allows the patient to absorb levodopa at a more or less constant rate. This implies that levodopa can be delivered to the brain at a relatively constant rate, which is presumed to help patients achieve a more normal physiological state. In patients treated with LCIG, it is generally possible to reduce or even discontinue the oral medications the patient was previously receiving.

The patient most likely to benefit from LCIG is one with moderately advanced levodopa-responsive PD (disabled, but ambulatory and at least semi-independent) whose waking hours are characterized by frequent fluctuations between the “on” and “off” states despite receiving optimized therapy with existing drugs. Identifying a patient as such would be part of routine neurological follow-up. In some centres, where neurosurgical expertise is available, DBS might be considered an option in such patients. In some instances, the patient’s wishes or general medical condition may make either DBS or jejunostomy tube placement impossible, and the only option may be to continue on optimized oral medication. The potential benefits of LCIG would need to be weighed against the inconvenience and potential complications of insertion and living with a jejunostomy tube and infusion pump. The jejunostomy tube insertion requires collaboration with an endoscopist (gastroenterologist or surgeon), implying added cost to the health care system; follow-up of patients requires some expertise with the maintenance of the infusion pump. Otherwise, the use of Duodopa would not require any new or specific diagnostic testing. At follow-up visits, the patient’s functional status would be assessed to ensure that LCIG is still providing benefit. If in doubt, the infusion rate could be reduced and the impact on function observed directly, usually during a day-long clinic visit.

Conclusions

A previous review of the use of LCIG for PD in 2009 by CDR led to the recommendation by CEDAC that LCIG "not be listed" due to the manufacturer's reported incremental cost per QALY and limitations in the quality of two trials (i.e., their open-label design, small sample sizes, high proportions of withdrawals, administration through an NJ tube, and inclusion of a patient population that was not representative of the target PD population that would be considered for LCIG treatment in Canadian clinical practice).

The CDR systematic review included one DB, double-dummy, phase III, active-controlled RCT (Study 001/002) designed to assess the benefits and harms of LCIG compared with IR OLC and one non-comparative, multinational, multi-centre, open-label, long-term safety study (Study 004) designed to assess the harms of LCIG for the treatment of patients with advanced levodopa-responsive PD who do not have satisfactory control of severe, debilitating motor fluctuations and hyper-/dyskinesia despite optimized treatment with available combinations of PD medicinal products, and for whom the benefits of this treatment may outweigh the risks associated with the insertion and long-term use of the PEG-J tube required for administration.

Compared with IR OLC, LCIG was associated with a statistically significant and clinically meaningful reduction in daily normalized "off" time at week 12 (the primary outcome) completed through the PDHD (Study 001/002). Overall, LCIG was also associated with a statistically significant improvement in daily normalized "on" time without troublesome dyskinesia at week 12 (Study 001/002). The results were primarily driven by the increase in "on" time without dyskinesia, whereas the change in "on" time with non-troublesome dyskinesia was not statistically significant. These results continue to support the benefit associated with LCIG treatment given that the results are being driven by the more desirable component ("on" time without dyskinesia). In general, patients treated with LCIG in Study 004 experienced a significant improvement in daily normalized "off" time and "on" time at week 54 compared with their baselines. The results of other secondary end points adjusted for multiple statistical testing used to assess PD symptoms at week 12 (i.e., the PDQ-39 summary index score and the UPDRS Part II) were also supportive of the primary analysis, demonstrating statistically significant and clinically meaningful improvement in favour of treatment with LCIG (Study 001/002).

Given that the comparator group in Study 001/002 also included levodopa/carbidopa as a treatment, between-treatment AE differences related to LCIG were not expected. Generally, AEs reported in Study 001/002 were known AEs of levodopa/carbidopa (e.g., depression, anxiety, confusion). Furthermore, the safety profile of the patients treated with LCIG in Study 001/002 was also similar to that of patients with advanced PD who have undergone a PEG-J procedure. The long-term safety of LCIG was explored in Study 003 and Study 005 (both open-label safety extension studies of Study 001/002 and/or Study 004 in which patients were treated with open-label LCIG for up to 60 months); the results suggest continued efficacy and no new safety signals compared with baseline.

Appendix 1: Patient Input Summary

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

1. Brief Description of Patient Group(s) Supplying Input

Three patient groups submitted input for this CADTH Common Drug Review (CDR): the Parkinson Association of Alberta (PAA), the Parkinson Society British Columbia (PSBC), and Parkinson Canada (PC).

PAA is an Alberta-based, registered charitable organization that provides support services, education, information/resources, referrals, and programs to patients with Parkinson disease (PD) and/or a Parkinson-plus syndrome, their families and care partners, health care professionals, community partners, and the general public. PAA funds innovative research in support of PD and receives its funds in the form of donations and fundraising activities.

PSBC was established in 1969 and provides advocacy, education, research, and support services for patients with PD. This organization receives donations from individuals, members, corporations, foundations, and fundraising.

PC is a national registered charity established in 1965 that provides advocacy, support services, and education for people living with Parkinson disease, their families, and their health care professionals. It also funds research programs for better treatments and a cure for PD.

None of the organizations declared any conflict of interest, other than receiving financial support from AbbVie in the past two years. PAA received between $10,001 and $50,000; PC and PSBC each received between $5,001 and $10,000.

2. Condition-Related Information

All three organizations gathered information through surveys (online or otherwise) and telephone or in-person interviews:

- PAA conducted a province-wide online survey between February 23, 2018 and March 1, 2018 that resulted in 41 responders. All but one responder were from Alberta; the majority were living in urban areas (49%) and had PD (68%); the rest were their care partners. Telephone interviews were conducted to collect information from 10 PD patients and their caregivers (five each) who had experience with Duodopa.
- PSBC conducted a provincial online survey and had 56 responders, including patients with advanced PD and their care partners. In addition, personal interviews were conducted with five patients who received Duodopa and their caregivers.
- PC conducted a survey between June 2017 and July 2017 with more than 850 responders representing all provinces and territories, of which 61% were patients with PD; the remainder were caregivers. Furthermore, 11 telephone interviews were conducted to gather information on Duodopa use.

PD is a progressive neurodegenerative disease of the nervous system that manifests in an inability to move normally; symptoms vary across patients. The most common symptoms are tremor while at rest, rigidity, slowness of movement, postural instability, and swallowing problems. Other symptoms include hypomimia, hypophonia, micrographia, changes in mind, mood, and memory, difficulties with sleep, constipation, pain, and fatigue. These

symptoms negatively affect patients' overall quality of life (QoL) as well their confidence and independence, socialization, relationships, recreational and everyday activities, and work. A distinct problem that many PD patients experience is "off" episodes, predominantly resulting from medication "wearing off" (i.e., the effect of medication stops), causing a resurgence of motor and non-motor Parkinson's symptoms (e.g., freezing episodes, tremor, mood swings, panic attacks, etc.). These "off" episodes can vary in frequency and are not always predictable; therefore, significant preplanning is required. When asked to rank the PD symptoms that the patients considered most important to control or manage, patients in the PC survey responded with the following outcomes: slowness and stiffness, impaired balance, cognitive changes and memory, and rigidity of the muscles. On the other hand, the PAA survey responders reported that mood changes and difficulties with sleeping, swallowing, and speech were the most important symptoms to control, also indicating cognitive impairments and bladder and bowel issues.

"I spend approximately 65% of my waking day in the 'off' state when my medication is not working. This causes me to have difficulty moving independently, feeding myself, and performing basic tasks. The 35% I manage in the 'on' state is with troublesome dyskinesia, very violent movements that again prevent me from doing most activities."

"I suffer from rigidity, bradykinesia, dystonia, tremor, and more recently, freezing while off. I fell and hurt my hip recently due to a freezing episode in the night when I was up to the washroom. Due to my low weight and new freezing, there is a real concern of a serious fall resulting in a fracture, which could lead to a further decline in my condition and the need for community support or an increased level of care."

"I have a hard time with all aspects of daily life (recreational, meal prep, have to cancel planned activities with family and friends) because of the following: very low energy, fall asleep unexpectedly, emotional, difficulty walking for prolong period, hard time moving my body at night in bed."

3. Current Therapy-Related Information

Currently available therapies to minimize PD symptoms include pharmacotherapy (e.g., levodopa, carbidopa), non-pharmacotherapy (e.g., deep brain stimulation [DBS]), rehabilitation therapy (e.g., physiotherapy, occupational therapy, speech therapy, and exercise) and psychotherapy (e.g., counselling). A balance between the side effects and benefits of the treatments often becomes more difficult with time as the disease progresses.

"The difference between optimal versus ineffective therapy may be the difference between a nursing home and independent living."

The majority of respondents were on oral medications as part of their treatment options. While medications were necessary to control symptoms and improve functioning, a number of side effects were reported, including disturbed sleep, nausea, constipation, dyskinesia, fatigue, and hallucinations. Others reported difficulties in administering treatment, including overdosing, swallowing, pain, reduced impulse control, and interference with protein-based food. In addition, an increasing reliance on treatment and adjustments in dosage were necessary with disease progression. Due to complicated, frequent, and variable dosing throughout the day (based on symptom severity and fluctuations between "on" and "off" states), compliance with treatment is difficult to ensure.

Rehabilitation and counselling sessions were a common form of therapy among patients to support their physical and mental well-being; however, lack of motivation, wait times, and

difficulties with communication were reported as a drawback of these therapies. In addition, treatment "wearing off" was reported to occur more quickly with vigorous exercise or intensive mental activity.

DBS is a surgically implanted neurostimulator (similar to a heart pacemaker) that delivers electrical stimulation to targeted areas in the brain that control movement, blocking the abnormal nerve signals that cause tremor and other PD symptoms. While DBS restores patients' ability to work and reduces or eliminates the need for medication, there is a considerable waitlist for the treatment. In some cases, the wait may be to five years, by which time a patient may no longer be an eligible candidate due to worsening symptoms.

Duodopa is a levodopa and carbidopa combination in the form of a gel that is delivered continuously throughout the day with a pump through a percutaneous endoscopic gastrostomy-jejunostomy (PEG-J) tube. This type of treatment is intended for use in patients with advanced PD who have severe and disabling motor symptoms that cannot be well controlled with currently available therapies. While this form of treatment results in a reduction in PD symptoms and fluctuations in "on" and "off" times, a number of factors significantly limit its accessibility to patients, including: the high cost of treatment, multiple hospital visits for surgery and titration, long wait-lists, lack of integration between PD specialists and general health care providers, and a shortage of appropriate health care professionals, particularly outside of big cities.

"Cost, constantly travelling to drug store to pick up something as the insurance company only releases the coverage dependent of the individual cost. Very frustrating to have to drive back and forth 4x to get the pills I need for my husband every month."

4. Expectations About the Drug Being Reviewed

Survey respondents expected a number of improvements that current therapies do not presently provide, either adequately or at all. A common expectation of new treatments across the patient groups was durable response that lasts longer and limits or eliminates "off" episodes. The majority of patients also highlighted their desire to have improved PD symptoms while minimizing treatment-associated side effects, such as dyskinesia, constipation, hallucination, sleep disturbances, and dystonia.

"My main focus is on quality of life and I weigh the benefit of the treatment in terms of having less off periods and the ability to enjoy life as fully as possible."

"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."

Patients included in the surveys who had experience with Duodopa had received it through provincial insurance or their neurologists. The clinical benefit of Duodopa was a common theme among all experienced responders. Patients reported that Duodopa had an instantaneous effect on their physical symptoms, including a reduction in dyskinesia and stiffness and improvements in speech, walkability, and balance. The use of Duodopa resulted in a decrease in (or the complete elimination of) "off" times. It also replaced oral medications entirely or partially reduced the dosage, resulting in more time for patients to travel, socialize, perform chores, and engage in pastimes, thereby improving their overall QoL.

A few side effects were noted by some patients, including constipation, frequent freezing, dizziness, and headache. Duodopa was considered relatively easy to use compared with oral medications or prior therapies; however, a few discomfort-causing issues related to the device or procedure were reported. Notably among these were the size and weight of the pump, difficulty when dressing, special consideration when showering or swimming, the need to clean the tube daily, the need to change the battery regularly, and infections and itchiness at the stoma. In addition, travelling was inconvenient, as cassettes need to be refrigerated. However, patients unanimously stated that the clinical benefits outweighed the side effects and complications related to the device or the procedure.

"It's made a huge difference in my quality of life. This doesn't fix Parkinson's, but because the medication goes directly into my brain in small doses every minute, it evens things out more, and I'm not tied to my watch." The care partner of this patient stated- "Now she has less dyskenisa and can press a button and the tremor goes away in 15-20 minutes. No more watch, life is good. I spend 5 minutes in the morning getting a new cartridge and 5 minutes at night flushing the tubes. That' is it."

"I'm always 'on' when I am plugged in to my pump! I have energy and motivation to try and live a reasonably normal life. It's miraculous! My mood is much better knowing that the medication is infusing into me at a regular, constant rate; I don't have to wonder if the next dosage of oral meds is going to get absorbed and work for me."

5. Additional Information

Given the nature of PD symptoms, almost all aspects of patients' lives are affected by the disease. Access to medications that minimize symptoms, side effects, and unpredictable "off" periods are crucial to patients' daily functioning and QoL. Given its exceptional benefits, the request for coverage for Duodopa was shared by all patient groups to ensure its affordability and accessibility, which would otherwise pose a significant economic burden on the patients and their families, since many of them have to leave the workforce or reduce their work hours as the disease progresses.

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations Note: Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	February 22, 2018
Alerts:	Bi-Weekly search updates until July 12, 2018
Study Types:	No search filters were applied
Limits:	No date limits; No language limits Human filter was applied Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	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#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading Word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.po	Population group [PsycInfo only]
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY

#	Searches
1	(duodopa* or duopa* or (carbidopa* adj4 levodopa*) or (carbidopa* adj4 L-dopa*) or carbilev* or CHF 1512 or co-careldopa* or DM 1992 or dopabain* or "IPX 066" or IPX066 or isicom or rytary* or tidomed* or numient* or nacom* or "ND 0612" or ND0612 or parcopa* or sinemet*).ti,ab,ot,kf,hw,rn,nm.
2	carbidopa/
3	(carbidopa* or carbidopum or methyldopahydrazine* or methyldopa-hydrazine* or alpha-methyldopahydrazine* or alpha-methyl-dopa-hydrazine* or alpha-methyl-alpha-hydrazinodopa* or lodosin* or lodosyn* or carboxydopa* or hydrazinomethyldopa* or CCRIS5093 or n-aminomethyldopa or KR87B45RGH or MK-486 or MK 486 or MK486 or MK 485 or MK-485 or MK485).ti,ab,ot,kf,hw,rn,nm.
4	2 or 3
5	levodopa/
6	(levodopa* or levodopum* or L-dopa or larodopa* or levodopa* or levopa* or levopa* or dopaflex* or dopar* or bendopa* or berkdopa* or biodopa* or brocadopa* or cerepap* or cerepar* or cidandopa* or deadopa* or dopa* or dopar* or dopaflex* or dopaidan* or dopal* or dopalina* or dopasol* or dopaston* or dopastral* or doprin* or doparkine* or eldopal* or eldopar* or eldopatec* or eurodopa* or helfo dopa or helfo-dopa or helfodopa* or inbrija* or insulamina* or maipedopa* or pardopa* or prodopa* or rigakin* or rigikin* or rigitrem* or speciadopa* or sobiodopa* or syndopa* or veldopa* or CCRIS 3766 or CVT-301 or HSDB 3348 or NSC 118381 or Ro 4-6316 or 46627O600J).ti,ab,ot,kf,hw,rn,nm.
7	5 or 6
8	4 and 7
9	1 or 8
10	gels/ or infusions, parenteral/
11	(gel or gels or gelatum or jell).ti,ab,ot,kf,hw.
12	(tube* or enteral or intraduodenal or infusion* or (continuous adj3 (delivery or administration or treatment)) or pump* or gastrostomy or jejunostomy or gastrojejeunostomy or duodenal or parenteral or duodenum or intubation or jejunal or ((PEG-J or PEG) adj4 tube) or (NJ adj4 tube)).ti,ab,ot,kf,hw.
13	10 or 11 or 12
14	9 and 13
15	14 use medall
16	*carbidopa plus levodopa/
17	(duodopa* or duopa* or (carbidopa* adj4 levodopa*) or (carbidopa* adj4 L-dopa*) or carbilev* or CHF 1512 or co-careldopa* or DM 1992 or dopabain* or "IPX 066" or IPX066 or isicom or rytary* or tidomed* or numient* or nacom* or "ND 0612" or ND0612 or parcopa* or sinemet*).ti,ab,ot,kw.
18	16 or 17
19	*carbidopa/
20	(carbidopa* or carbidopum or methyldopahydrazine* or methyldopa-hydrazine* or alpha-methyldopahydrazine* or alpha-methyl-dopa-hydrazine* or alpha-methyl-alpha-hydrazinodopa* or lodosin* or lodosyn* or carboxydopa* or hydrazinomethyldopa* or CCRIS5093 or n-aminomethyldopa or KR87B45RGH or MK-486 or MK 486 or MK486 or MK 485 or MK-485 or MK485).ti,ab,ot,kw.
21	19 or 20
22	*levodopa/
23	(levodopa* or levodopum* or L-dopa or larodopa* or levodopa* or levopa* or levopa* or dopaflex* or dopar* or bendopa* or berkdopa* or biodopa* or brocadopa* or cerepap* or cerepar* or cidandopa* or deadopa* or dopa* or dopar* or dopaflex* or dopaidan* or dopal* or dopalina* or dopasol* or dopaston* or dopastral* or doprin* or doparkine* or eldopal* or eldopar* or eldopatec* or eurodopa* or helfo dopa or helfo-dopa or helfodopa* or inbrija* or insulamina* or maipedopa* or pardopa* or prodopa* or rigakin* or rigikin* or rigitrem* or speciadopa* or sobiodopa* or syndopa* or veldopa* or CCRIS 3766 or CVT-301

MULTI-DATABASE STRATEGY	
#	**Searches**
	or HSDB 3348 or NSC 118381 or Ro 4-6316 or 46627O600J).ti,ab,ot,kw.
24	22 or 23
25	21 and 24
26	18 or 25
27	exp gel/ or exp parenteral drug administration/
28	(gel or gels or gelatum or jell).ti,ab,ot,kw.
29	(tube* or enteral or intraduodenal or infusion* or (continuous adj3 (delivery or administration or treatment)) or pump* or gastrostomy or jejunostomy or gastrojejeunostomy or duodenal or parenteral or duodenum or intubation or jejunal or ((PEG-J or PEG) adj4 tube) or (NJ adj4 tube)).ti,ab,ot,kw.
30	27 or 28 or 29
31	26 and 30
32	31 use oemezd
33	conference abstract.pt.
34	32 not 33
35	15 or 34
36	exp animals/
37	exp animal experimentation/ or exp animal experiment/
38	exp models animal/
39	nonhuman/
40	exp vertebrate/ or exp vertebrates/
41	or/36-40
42	exp humans/
43	exp human experimentation/ or exp human experiment/
44	or/42-43
45	41 not 44
46	35 not 45
47	remove duplicates from 46

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

Grey Literature

Dates for Search:	February 2018
Keywords:	Duodopa (carbidopa and levodopa), motor fluctuations in patients with advanced Parkinson's disease
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist, Grey matters: a practical tool for evidence-based searching (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters) were searched:

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

Appendix 3: Excluded Studies

Reference	Reason for Exclusion
ANTONINI et al. (2016)[72]	Study population – Irrelevant
GUTHIKONDA et al. (2014)[73]	Study design – Irrelevant
JUGEL et al. (2013)[74]	Study outcome – Irrelevant
KURTH et al. (1993)[75]	Intervention – Irrelevant
KARLSBORG et al. (2010)[76]	Study design – Irrelevant

Appendix 4: Detailed Outcome Data

Table 22: Summary of "Off" Time Sensitivity Analyses (Full Analysis Set)

End Point	Study 001/002			
	Adjusted LS Mean Change From Baseline at Week 12 (SE)			
	LCIG + PBO IR OLC Capsules	PBO LCIG + IR OLC Capsules	Adjusted LS MD in Change From Baseline (95% CI)	*P* value
Off time, hours per day				
MMRM for imputed data[a]	–4.09 (0.55)	–2.25 (0.56)	–1.84 (–2.98 to –0.70)	0.0021
Off time, hours per day (LOCF)[b]				
Without covariate of rescue medication on valid PDHD days	–4.02 (0.65)	–2.13 (0.66)	–1.89 (–3.03 to –0.75)	0.0016
With covariate of rescue medication over the treatment period	–4.02 (0.65)	–2.14 (0.66)	–1.88 (–3.03 to –0.73)	0.0018
With values on final PDHD days with rescue medication use replaced by average daily normalized "off" time at baseline	–3.29 (0.70)	–1.47 (0.70)	–1.82 (–3.05 to –0.60)	0.0042
Excluding values on final PDHD days with rescue medication use	–4.30 (0.68)	–2.52 (0.69)	–1.78 (–2.97 to –0.58)	0.0043

ANCOVA = analysis of covariance; CI = confidence interval; IR = immediate-release; LCIG = levodopa/carbidopa intestinal gel; LOCF = last observation carried forward; LS = least squares; MD = mean difference; MMRM = mixed-effects models for repeated measures; OLC = oral levodopa/carbidopa; PBO = placebo; PDHDD = Parkinson disease home diary; SE = standard error.

Note: The diary is completed every 30 minutes for the full 24 hours of each of 3 days prior to selected clinic visits. It reflects both time awake and time asleep. Daily totals are normalized to a 0 to 16-hour scale (i.e., 16 hours of awake time). The normalized totals for the 3 days prior to the visit are averaged for the analysis.

[a] LS means, SE, CI, and *P* values are based on a repeated measures linear regression model of the change from baseline score, with fixed effects for country, study week as a categorical variable, baseline score, treatment, treatment by study week, and baseline by study week interactions, assuming an unstructured covariance matrix.

[b] Treatment comparisons are based on an ANCOVA model including effects for treatment, country, and with the corresponding baseline as covariates.

Source: Study 001/002 Clinical Study Report.[26]

Table 23: Summary of Absolute "On" "Off" Time (Full Analysis Set)

End Point	Study 001/002	
	LCIG + PBO IR OLC Capsules N = 36	PBO LCIG + IR OLC Capsules N = 33
Absolute "off" time, hours per day		
Baseline, n (%)	35 (97)	31 (94)
Baseline, mean (SD)	6.63 (2.08)	7.51 (2.74)
Adjusted LS mean change from baseline at week 12 (SE)	–4.46 (0.74)	–2.18 (0.74)
Adjusted LS mean difference in change from baseline versus comparator (95% CI)	–2.28 (–3.58 to –0.98), *P* = 0.0009	
Absolute "on" time without troublesome dyskinesia, hours per day		
Baseline, n (%)	35 (97)	31 (94)
Baseline, mean (SD)	9.09 (2.26)	8.64 (2.29)
Adjusted LS mean change from baseline at week 12 (SE)	4.08 (0.78)	2.48 (0.79)

End Point	Study 001/002	
	LCIG + PBO IR OLC Capsules N = 36	PBO LCIG + IR OLC Capsules N = 33
Adjusted LS mean difference in change from baseline versus comparator (95% CI)	1.60 (0.25, 2.95), *P* = 0.0207	
Absolute "on" time without dyskinesia, hours per day		
Baseline, n (%)	35 (97)	31 (94)
Baseline, mean (SD)	6.63 (2.77)	6.24 (3.32)
Adjusted LS mean change from baseline at week 12 (SE)	3.29 (1.11)	1.10 (1.11)
Adjusted LS mean difference in change from baseline versus comparator (95% CI)	2.19 (0.28 to 4.11), *P* = 0.0255	
Absolute "on" time with non-troublesome dyskinesia, hours per day		
Baseline, n (%)	35 (97)	31 (94)
Baseline, mean (SD)	2.46 (1.92)	2.41 (2.19)
Adjusted LS mean change from baseline at week 12 (SE)	1.01 (0.88)	1.77 (0.88)
Adjusted LS mean difference in change from baseline versus comparator (95% CI)	–0.77 (–2.29 to 0.76), *P* = 0.3183	
Absolute "on" time with troublesome dyskinesia, hours per day		
Baseline, n (%)	35 (97)	31 (94)
Baseline, mean (SD)	0.99 (1.63)	1.08 (1.55)
Adjusted LS mean change from baseline at week 12 (SE)	–0.07 (0.57)	0.04 (0.57)
Adjusted LS mean difference in change from baseline versus comparator (95% CI)	–0.11 (–1.09 to 0.87), *P* = 0.8274	

ANCOVA = analysis of covariance; CI = confidence interval; IR = immediate-release; LCIG = levodopa/carbidopa intestinal gel; LS = least squares; OLC = oral levodopa/carbidopa; PBO = placebo; SD = standard deviation; SE = standard error.

Note: The diary is completed every 30 minutes for the full 24 hours of each of 3 days prior to selected clinic visits. It reflects both time awake and time asleep. Daily totals are normalized to a 0-hour to 16-hour scale (i.e., 16 hours of awake time). The normalized totals for the 3 days prior to the visit are averaged for the analysis.

Treatment comparisons are based on an ANCOVA model including effects for treatment and country and using the corresponding baseline as covariates.

Source: Study 001/002 Clinical Study Report.[26]

Appendix 5: Validity of Outcome Measures

Aim

To summarize the validity of the following outcome measures:

- Parkinson disease home diary (PDHD)
- 39-Item Parkinson's Disease Questionnaire (PDQ-39)
- Clinical Global Impression – Improvement (CGI-I)
- Unified Parkinson's Disease Rating Scale (UPDRS)
- EuroQol 5-Dimensions 3-Levels (EQ-5D-3L) questionnaire
- Zarit Burden Interview (ZBI)

Findings

Table 24: Validity and Minimal Important Differences of Outcome Measures

Instrument	Type	Evidence of Validity	MCID	References
Parkinson Disease Home Diary	The PDHD is a PD diary for patients experiencing motor fluctuations and dyskinesia. It records the amount of "on" and "off" time over 24 hours. It consists of 5 categories: (1) asleep, (2) "off," (3) "on" without dyskinesia, (4) "on" with non-troublesome dyskinesia, and (5) "on" with troublesome dyskinesia.	Construct validity and reliability evaluated in a single study	"Off" time: 1 hour (patients with motor fluctuation) 1 to 1.3 hours (APD)	61,63,77
Parkinson's Disease Questionnaire-39	The PDQ-39 is a disease-specific HRQoL measure consisting of eight domains (mobility, activities of daily living, 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 Mobility: –3.2 ADL: –4.4 Emotional well-being: –4.2 Stigma: –5.6 Social support: –1.4 Cognition: –1.8 Communication: –4.2 Pain: –2.1	62,78-106
Clinical Global Impression	The CGI is a generic assessment of the clinician's view of the patient's global functioning, and consists of 3 components: Severity of Illness (CGI-S), Global Improvement (CGI-I), and Efficacy Index (CGI-E). The CGI-I subscale is graded on a 7-point scale (1 = very much improved; 7 = very much worse).	No information on the validity and reliability of the CGI-I subscale	Unknown in PD patients	107,108
Unified Parkinson's Disease Rating Scale	Measure of disability and impairment in PD. Four parts: Part I (mentation, behaviour, and mood: four items, score 0 to 16); Part II (activities of daily living; 13 items, score 0 to 56 for each state); Part III (motor examination; 14 items, score 0 to 108); and Part IV (complications of therapy in past week; 11 items, score 0 to 23). Total score from 0 (best) to 199 (worst).	Yes	Total score: 3 to 8 points (EPD); 4.1 to 17.8 (all stages) Part II: 0.5 to 3.0 points (EPD) and 1.8 to 2.3 points (APD) Part III: 2.0 to 6.2 points (EPD) and 5.2 to 6.5 points (APD)	61,63,109-126

Instrument	Type	Evidence of Validity	MCID	References
EuroQol 5-Dimensions 3-Levels	The EQ-5D-3L is a generic, preference-based, HRQoL measure consisting of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels representing no problems (1), some problems (2), and extreme problems (3).	Yes	Index score range: 0.10 to 0.11	64,127-130
Zarit Burden Interview	The ZBI is a generic self-reported measure to assess caregiver burden. It consists of 22 items measured on a 5-point Likert scale. Scores of individual items range from 0 (never) to 4 (nearly always); total score ranges between 0 and 88, with a higher score representing more burden.	Yes, limited information on reliability	Unknown in caregivers of patients with PD	35,131-135

ADL = activities of daily living; APD = advanced Parkinson disease; CGI-E = Clinical Global Impression – Efficacy Index; CGI-I= Clinical Global Impression – Improvement; CGI-S= Clinical Global Impression – Severity of Illness; EPD = early Parkinson disease; EQ-5D-3L = EuroQol 5-Dimensions 3-Levels questionnaire; HRQoL = health-related quality of life; MCID = minimal clinically important difference; PD = Parkinson disease; PDHD = Parkinson disease home diary; PDQ-39 = 39-item Parkinson's Disease Questionnaire; ZBI = Zarit Burden Interview.

Evidence from validation studies is summarized for all instruments according to the following metrics and depending on information availability: comprehensiveness (i.e., how well the measure captures the areas of health-related quality of life [HRQoL] relevant to patients with Parkinson disease [PD]); feasibility (i.e., duration and ease of administration in different settings); validity (i.e., content, construct [convergent, discriminant], and criterion [concurrent, predictive] validity); reliability (internal consistency; i.e., inter-item correlations); reproducibility (i.e., test–retest [inter/intra-rater] reliability); responsiveness (sensitivity to detecting meaningful changes over time); floor and ceiling effects (i.e., the extent to which respondents score at the bottom or top of a scale); and scaling assumptions (i.e., correctly grouping items into scales and summing them to produce a score with or without weighing or standardizing).

Interpretation of the reliability and validity metrics were based on the following criteria:

- Inter/intra-rater reliability/agreement (kappa statistics or interclass coefficient [ICC]): < 0 to 0.2 = poor; 0.21 to 0.4 = fair; 0.41 to 0.6 = moderate; 0.61 to 0.8 = substantial; 0.81 to 1.00 = almost perfect agreement[136]
- Internal consistency (Cronbach's alpha) and test–retest reliability (≥ 0.7 is considered acceptable)[137]
- Validity; i.e., between-scale comparison (correlation coefficient, r): ≤ 0.3 = weak, 0.3 to ≤ 0.5 = moderate, > 0.5 = strong)[138]

The Parkinson Disease Home Diary

The PDHD is a self- or caregiver-administered diary that patients with PD experiencing motor fluctuations and dyskinesia can fill out during their participation in a clinical trial. This diary aims to assess the amount of "on" and "off" time that patients experience in a 24-hour period.[77] The PDHD consists of five distinctive states: (1) asleep; (2) "off;" (3) "on" without dyskinesia; (4) "on" with non-troublesome dyskinesia; and (5) "on" with troublesome dyskinesia. [77]

The PDHD was only validated in a single study conducted among 302 patients from 10 countries with idiopathic PD who were experiencing motor fluctuations and dyskinesia and capable of accurately completing the diaries.[77] The diary was shown to be both feasible and simple in its use (with an 83% completion rate without duplication or error);[77] however, errors and non-compliance were more prevalent after three days of use. The adaptability of the PDHD for non-English speakers was further demonstrated after the diary was translated from English into study participants' native languages. The PDHD displayed substantial reliability (mean ICC: 0.71; mean correlation between any two days: 0.74); test–retest reliability improved as the number of diary days increased (Cronbach's alpha > 0.8 for comparisons between two or more diary days). Finally, a moderate correlation was observed between other visual analogue scale (VAS) measures and corresponding PDHD measures when they were compared (Pearson correlation coefficients ranged from 0.36 to 0.57); thus, acceptable construct (concurrent) validity was shown.[77] The major limitation of the study includes comparing the validity of PDHD against only one patient-reported functional measure (VAS) without other external measures of function and disability.

Minimal Clinically Important Difference

Hauser et al. analyzed data from a placebo-controlled, randomized controlled trial (RCT) that included patients with motor fluctuations (N = 472); the total duration was six months. Using the Clinical Global Impression — Improvement (CGI-I) as an anchor, they reported a minimal clinically important difference (MCID) of a one-hour reduction in self-rated "off" time.[61] Using data from another double-dummy, placebo-controlled RCT among advanced PD patients (N = 517, 18 weeks), Hauser et al. estimated the MCID for "off" time with CGI-I and Patient Global Impression – Improvement (PGI-I) as anchors. Among advanced PD patients, the MCID for "off" time ranged from 1 hour to 1.3 hours.[63]

39-Item Parkinson's Disease Questionnaire

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 Disorder Society (MDS).[86] The PDQ-39 is a self-administered questionnaire consisting of 39 items that measure eight domains of health: mobility (10 items), activities of daily living (ADL; six items), emotional well-being (six items), stigma (four items), social support (three items), cognition (four items), communication (three items), and bodily discomfort (three items).[78] Each item is graded on a 5-point Likert scale (0 = never; 4 = always); the items 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 PD summary index [PDQSI]) representing the global HRQoL can be created by averaging the eight subscale scores. The PDQSI is also coded on a scale ranging from 0 to 100, with higher scores indicating worse quality of life (QoL).[78,82]

The psychometric properties of the domain and index scores of the PDQ-39 have been extensively evaluated in many studies across different geographic locations and with different languages, including Chinese, Estonian, French, Japanese, Korean, Portuguese, Persian, Spanish, and Swedish.[87-106] Only evidence for the English version of the scale is summarized here.

One study by Damiano et al. [80] assessed the comprehensiveness of PDQ-39 in a clinical trial setting based on literature review and through consultation with clinicians and patients.

The authors found that the PDQ-39 measures 10 out of 12 areas of HRQoL identified as relevant to PD patients other than self-image and sexual function.[80]

The Damiano et al. study reported that the PDQ-39 has a short administration time — estimated to be less than 30 minutes — and can be uniformly administered by patients, interviewers, or caregivers.[80] One study by Jenkinson et al. validated the PDQ-39 in a cross-cultural study across five countries (including Canada and the US).[83] As with the previous study, a high completion rate
(> 82%) and low percentage of missing scores (< 5%) was reported for both domain and index scores.[83] 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.[80]

The UK-based research group that developed the scale assessed the reliability of the PDQ-39 and PDQSI internally with other domain scores, and found an acceptable internal consistency (Cronbach's alpha > 0.7 and > 0.8, respectively), indicating the items performed well enough together to be a composite score. The test–retest reliability (range: 0.68 to 0.94) was high.[78,82] A US study adapted the British version into a US version and found high test–retest reliability (range 0.86 to 0.95) as well as corroborating psychometric properties, with Cronbach's alpha > 0.7 for all but one of the domains (social support, alpha = 0.51).[79] Similarly, adequate internal consistency was reported by Damiano et al.[84] (Cronbach's alpha ≥ 0.7 across domains and 0.85 for PDQSI), with the exception of social support (Cronbach's alpha = 0.57). Findings from the cross-national validation study were similar, with generally adequate internal consistency for all domains (Cronbach's alpha ≥ 0.7) except 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 the Hoehn and Yahr (HY) 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)[83]. In contrast, correlations between related domain scores of the PDQ-39 and Short Form (36) Health Survey (SF-36) were strong (–0.66 ≤ r ≤ – 0.8).[81] The US-based study reported similar findings, with strong correlations between related domain scores of the PDQ-39 and SF-36 (– 0.59 ≤ r ≤ – 0.88), with the exception of the subscale measuring social support (r = – 0.22).[79] In addition, the PDQ-39 generally had strong correlations with five measures of symptoms severity (tremor, stiffness, slowness, freezing, and jerking) as measured by related scales of the SF-36 (0.21 ≤ r ≤ 0.74).[79] Concurrent validity in the English version of the PDQ-39 was only assessed by Harrison et al. by comparing the performance of PDQ-39 with other established measures of disease severity, depression, and anxiety.[85] Domains of the PDQ-39 that were 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).[85]

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 domain of the PDQ-39 with progressive worsening of five measures of symptoms severity (tremor, stiffness, slowness, freezing, and jerking).[79] The discriminative ability was further demonstrated by Damiano et al. where higher (poorer)

PDQ-39 domain and index scores were associated with more severe HY stages and dyskinesia as well as the presence of comorbidities.[84]

The developers of the PDQ-39 reported moderate responsiveness for two of its domains (standardized mean change over time: 0.55 and 0.43 for mobility and ADL, respectively); responsiveness for the other six domains was low. [80] Harrison et al. assessed the comparative responsiveness of the PDQ-39 and other established measures of mood and motor function (the General Health Questionnaire-28 and the Office of Population and Census Surveys disability instrument) in a UK population.[85] Results from their study showed a superior responsiveness to of the PDQ-39 and its subscales to change over time (except domains involving emotion and bodily discomfort).

Damiano et al. evaluated floor and ceiling effects on patients with varying degrees of PD severity using self-completed and telephone interview versions of the PDQ-39. Both modes of administration generally showed low floor and ceiling effects across different domains (range: 0.0% to 6.1% for floor effects and 1.5 to 31.3% for ceiling effects); these were essentially eliminated by the index score. However, the stigma and social support subscale had noticeably high ceiling effects, indicating that a high proportion of study participants had maximum scores for these two domains.[84] These findings were consistent with the cross-national validation study,[83] where generally low floor and ceiling effects were seen across different domains (< 15% and 5%, respectively). However, the stigma and social support domains had large floor effects (> 20% and > 50%, respectively), indicating that 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.[83] 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 > 50% of the variance, supporting the scaling assumptions.

Minimal Clinically Important Difference

One study by the original research group that developed the PDQ-39 scale investigated the minimal important difference (MID) for the index score and across different domains. A postal survey of randomly selected patients from 13 local branches of the UK Parkinson's Disease Society was conducted; the response rate was 53% (N = 728). No information on PD severity or anchoring were provided. Findings from the study showed a varying mean MID for different domains: mobility (–3.2), ADL (–4.4), emotional well-being (–4.2), stigma (–5.6), social support (–11.4), cognition (–1.8), communication (–4.2), pain (–2.1), and overall score (–1.6).[62]

Clinical Global Impression – Improvement

The CGI scale is a generic measure that provides a brief, overall assessment of the clinician's view of the patient's global functioning, which is used to compare before- and after-treatment changes. It consists of three components: Severity of Illness (CGI-S), Global Improvement (CGI-I), and the Efficacy Index (CGI-E). Scores on the Severity of Illness subscale range from 1 ("not ill at all") to 7 ("among the most extremely ill"). The Global Improvement subscale is also rated on a 7-point scale where 1 = very much improved since the initiation of treatment; 2 = much improved; 3 = minimally improved; 4 = no change from baseline (the initiation of treatment); 5 = minimally worse; 6 = much worse; and 7 = very much worse since the initiation of treatment. Both the severity and improvement subscales

are companion one-item measures that generally track with each other such that improvement in one follows the other. However, the anchors for scoring are different; the CGI-I measures changes from baseline/pre-treatment, whereas the CGI-S measure changes from prior measure (which can be in the preceding week). Consequently, the two scores can occasionally be dissociated if there is a substantial lapse between the measures.[108,139]

No validation study was found for CGI-I specifically; and one international cross-sectional study by Martínez-Martín et al. evaluated the validity of CGI-S among PD patients.[107] In order to assess the construct validity, the CGI-S subscale was correlated with the HY stage, the Clinical Impression of Severity Index for Parkinson Disease (CISI-PD), and the Patient Global Impression-Severity (PGI-S). Correlations were high between CGI-S and HY stage and CISI-PD ($r > 0.80$), but relatively moderate between CGI-S and PGI-S ($r = 0.61$). In addition, the concordance between CGI-S and HY stage as well as CISI-PD was high across all stages of PD (78.5% and 84.3%) but moderate between CGI-S and PGI-S (61%). Concordance between tests for the severity levels of the four scales was further demonstrated by a moderate Kendall's coefficient of concordance and generalized kappa statistic (0.67 and 0.52, respectively). These findings are consistent with real-world scenarios, where ratings using patient-administered instruments are generally higher than clinician- or investigator-administered ones, accounting for the rather modest concordance indices.[107]

Minimal Clinically Important Difference

No information on the MCID of the CGI-I in patients with PD was found.

Unified Parkinson's Disease Rating Scale

The UPDRS is the standard instrument for measuring parkinsonian signs and symptoms. The scale is composed of four parts: Part I (mentation, behaviour, and mood; four items), Part II (ADL; 13 items), Part III (motor examination; 14 items), and Part IV (complications of therapy and symptoms including dyskinesia and "off" state; 11 items). Individual items in parts I to III are scored on a 5-point scale (0 to 4), with higher scores indicating worse symptoms, while Part IV includes a number of items scored either numerically (like parts I to III) or using zero or one (no or yes, respectively). The full scale takes 10 minutes to 20 minutes to administer with a range of 0 (no disability) to 199 (worst disability). The ranges of scores for the subscales are: 1) Mentation, Behaviour and Mood (0 to 16); 2) ADL (0 to 52); 3) Motor Examination (0 to 108); and 4) Complications of Therapy (0 to 23).[140] In addition, a number of subscales that assess specific signs of PD — including but not limited to tremor, rigidity, bradykinesia, and postural instability/gait disturbance — have been derived from combining certain items within the scale.[118]

The subscales, four sections, and overall score of the UPDRS have been thoroughly assessed in different languages, including Hebrew, Hungarian, Italian, Japanese, and Spanish, with clinic- and population-based samples of varying PD severity.[121-126] Despite the scale's comprehensive coverage of motor symptoms and wide utilization, there are a few notable weaknesses noted by the MDS, including limited non-motor screening items, "flaws and ambiguities" for some items, and inadequate instructions for raters.[117] The MDS commissioned a revision of the original scale in 2007, termed the MDS-sponsored UPDRS revision. The new version demonstrated improved psychometric properties in different settings in addition to large-scale comparisons with the original version.[111] However, the study included in this review used the original UPDRS; therefore, the psychometric

properties of the original version are summarized here. Due to abundant literature on the validity of UPDRS in different settings across the world, evidence for the English version of the original UPDRS and its subsections is presented here.

Full-Scale Assessment

Four studies assessed the measurement properties of the original UPDRS in patients with varying degrees of PD severity, including an early validation study by the Cooperative Multicentric Group,[119] one multi-centre RCT that included Canada and the US,[118] a systematic review of 11 measures of PD,[120] and a large, multi-centre, cross-sectional study.[113,115]

The Cooperative Multicentric Group reported that the administration time for the UPDRS was brief (10 minutes to 20 minutes).[119] The multi-centre study showed a low percentage of missing data across the four subscales (< 10%), indicating a high completion rate.[113,115] Together, these results demonstrate that the scale can be easily administered within a short period in clinical trial and population settings.

Across all studies, internal consistency was found to be adequate for the full scale as well as its subscales (0.79 ≤ Cronbach's alpha ≤ 0.96).[113,115,119,120] Studies assessing inter-rater reliability found moderate to high inter-rater agreements for most items (0.50 < kappa < 0.90) and fair for a few (0.40 < kappa < 0.50), with total scores highly correlated among raters (r = 0.98).[119,120] Additionally, a stable factor structure and high internal consistency was shown across "off" and "on" states for the UPDRS Part III.[120] Only one multi-centre trial (including Canada and the US) evaluated the test–retest/intra-rater reliability of the UPDRS as measured by neurologists among patients with early-stage PD (EPD). It reported excellent test–retest reliability for the total score (ICC 0.92) and substantial-to-excellent reliability for its subsections (ICC range: 0.74 to 0.90).[118] The individual items within the subsections had a varying degree of intra-rater reliability (weighted kappa range: 0.49 to 0.75); the lower scores were likely due to including patients with relatively mild symptoms.[118]

A panel of 13 international experts independently rated the relevance of the scales and items of the UPDRS to assess content validity, with endorsement by at least 75% of the experts needed to establish satisfactory content validity.[113] With the exception of the UPDRS Part III (83.3%), none of the subscales attained the adequate standard (endorsement rate: 40% to 50%). A similarly low proportion of items in UPDRS parts I, II, and IV achieved an adequate content validity compared with UPDRS Part III.[113] The systematic review by Ramakar et al. identified several key symptoms of motor impairment and disabilities affecting daily life and reported that these features were represented in the UPDRS motor examination and the ADL subscale, albeit unequally without any weighing.[120]

Criterion validity was assessed by one study, and a strong correlation was found between the UPDRS and HY scale (r = 0.71).[119] The same study assessed construct validity by comparing the UPDRS with other known measures of disability and functional impairment (convergent validity). Between-scale correlations were strong for the Intermediate Scale for Assessment of PD, the Schwab and England Scale (SES) (r > 0.80 for both), the Mini-Mental State Examination, and the Hamilton Scale for Depression (r = 0.53, 0.64, respectively).[119] Authors of the large multi-centre study also evaluated the construct validity of the UPDRS by examining its relationship with the HY score and SES. All four subscales showed moderate to strong correlations with both measures (0.4 < Irl < 0.75).[113,115] Findings from the systematic review were corroborating.[120]

The subscales' discriminative ability was supported by a linearly increasing trend in all subscale scores with the progression in HY stage.[113,115] For all subscales, observed and possible score ranges coincided, with no patients at the upper end of the UPDRS parts I, II, and IV. Large floor effects were seen for UPDRS parts I and IV (> 20%), and all scales reflected small ceiling effects

(< 1%).[113,115] This was likely due to the predominant inclusion of patients with milder symptoms, resulting in skewed data since patients in severe stages unable to participate in research studies were not adequately represented.[113,115] The scale, and in particular parts I and IV, may not adequately distinguish patients with milder symptoms if they score low on these subscales.

The multi-centre cross-sectional study reported that the item-total corrected correlations were satisfactory overall for all subscales (Part I, 0.57 to 0.66; Part II, 0.30 to 0.80; Part III, 0.25 to 0.74; and Part IV, 0.26 to 0.76); however, a few items within the ADL, motor, and complications-from-treatment subscale had lower correlations.[113,115] Similarly, in the earlier study, strong item-total correlations were found for most items ($0.60 < r < 0.81$) and low correlations for others ($0.22 < r < 0.50$), with lower consistency for items related to depression, motivation/initiative, and tremor.[119] Multi-trait scaling analysis showed a high scaling success rate for all four subscales (> 90%). Factor analysis in both studies showed all UPDRS items together explained almost 60% of the variance (58.5%).[113,115,119]

Part I (Mentation, Behaviour, and Mood)

A US-based study assessed the sensitivity and specificity as well as criterion validity (concurrent) by comparing related items of UPDRS Part I with criterion tests for dementia, psychosis, and depression; namely, the telephone interview for cognition status, psychiatric assessment for psychosis, and the geriatric depression scale. Overall, results for concurrent validity showed moderate to strong correlations with criterion measures ($0.38 \leq r \leq 0.66$). The discriminatory power of the test was fair (area under the receiver operating curve [AUROC] ~70%). However, low or modest ranges of sensitivity (19% to 0.61) and specificity (0.48 to 0.87) were found for the individual items on the subscale, even with an optimal cut-off point.[112]

Part II (Activities of Daily Living)

No study was found that reported the validity of the English version of UPDRS Part II specifically; however, one study conducted in Canada and the US assessed the investigator-patient (inter-rater) reproducibility of UPDRS parts I and II using clinical trial data. For assessments done at baseline and 12 months, substantial clinician–patient agreement was found for both UPDRS Part I and Part II (concordance correlation range: 0.6 to 0.7 and 0.78 to 0.81, respectively). Most items on the subscales achieved moderate agreement ($0.40 < \text{kappa} \leq 0.80$), with the exception of a few that were deemed to be due to limited response variability or subjective nature.[109]

Part III (Motor Examination)

One study by Metman et al. investigated the intra-rater reliability of the UPDRS Part III by clinicians in patients with advanced PD. In both "on" and "off" states, clinicians had excellent agreement in total UPDRS Part III score (ICC ~0.90).[116]

Part IV (Complications of Therapy and Symptoms)

No evidence specifically validating the UPDRS Part IV (English version) was available.

Minimal Clinically Important Difference

Schrag et al. estimated MCIDs for the UPDRS ADL, motor, and total scores retrospectively among patients with EPD using data from two independent, active-controlled RCTs (N = 603 total).[114] Using the CGI-I as an anchor, the minimal change representing the MCID following six months of anti-PD treatment was determined. They reported a mean change in 5 and 8 points on the UPDRS motor and total scores as the cut-off, respectively, corresponding to an HY stage of I to III. On the other hand, a mean change in 2 and 3 points on the UPDRS ADL score was found to be appropriate, corresponding to a HY stage of I/I.5 to II and II.5/III, respectively.[114]

Three other studies provided estimates of MCIDs for subscales and total score among patients with varying stages of PD. One cross-sectional study (N = 653, representing all PD stages) used both distribution and anchor-based (based on SES, HY stage, and Short Form (SF)-12) approaches and reported MCIDs of 2.3 points for the UPDRS motor score and 4.1 points for the total score.[110] Hauser et al. analyzed data from two separate, placebo-controlled RCTs that included EPD patients (N = 404) and patients with motor fluctuations (N = 472); total duration was six months. Using the CGI-I as an anchor, they reported an MCID of 0.5 to 0.7 points for the ADL score, 2 to 2.4 points for the motor score, and 3 to 3.5 points for the total score (I to III).[61] Using data from two other double-dummy, placebo-controlled RCTs among EPD patients (N = 539, 33 weeks) and APD patients (N = 517, 18 weeks), Hauser et al. estimated the MCIDs for UPDRS parts II and III using the CGI-I and PGI-I as anchors. Among EPD patients, the range of MCIDs for UPDRS parts II and III was 1.8 to 2 points and 6.1 to 6.2 points, respectively. Among APD patients, the range of MCIDs for UPDRS parts II and III was 1.8 to 2.3 points and 5.2 to 6.5 points, respectively.[63]

EuroQol 5-Dimensions 3-Levels

The EQ-5D-3L is a generic, preference-based HRQoL instrument that has been applied to a wide range of health conditions and treatments, including PD.[127,128] The first of two parts of the EQ-5D-3L is a descriptive system that classifies respondents (aged ≥ 12 years) into one of 243 distinct health states. The descriptive system consists of the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three possible levels (1, 2, or 3) representing “no problems,” “some problems,” and “extreme problems,” respectively. Respondents are asked to choose one level that reflects their own health state for each of the five dimensions. A scoring function can be used to assign a value (EQ-5D-3L index score) to self-reported health states from a set of population-based preference weights.[127,128] The second part is a 20 cm visual analogue scale (EQ VAS) that has end points labelled 0 and 100, with respective anchors of “worst imaginable health state” and “best imaginable health state,” respectively. Respondents are asked to rate their own health by drawing a line from an anchor box to the point on the EQ VAS that best represents their own health on that day. The EQ-5D-3L produces three types of data for each respondent:

- a profile indicating the extent of problems on each of the five dimensions represented by a five-digit descriptor, such as 11121, 33211, etc.
- 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-3L index score is generated by applying a multi-attribute utility function to the descriptive system. Different utility functions are available that reflect the preferences of specific populations (e.g., US or UK). The lowest possible overall score (corresponding to

severe problems on all five attributes) varies depending on the utility function that is applied to the descriptive system (e.g., −0.59 for the UK algorithm and −0.109 for the US algorithm). Scores less than 0 represent health states that are valued by society as being worse than dead, while scores of 0 and 1.00 are assigned to the health states "dead" and "perfect health," respectively. There is a five-level version of the EQ-5D (the EQ-5D-5L) that is now available. It is also commonly used.[127,128]

The EQ-5D has been extensively validated across countries around the world and in various conditions; however, its validity in patients with PD is relatively sparse. A systematic review by Xin et al. assessed the construct validity (convergent validity and discriminative ability) and responsiveness of the instrument in patients with PD.[64] Results from six studies showed that the correlations between the EQ-5D-3L index score and the PDQ-8 summary score, HY staging, and UPDRS total score was strong (r = –0.75), moderate (–0.32 < r < –0.53), and moderate to strong (0.39 < |r| < 0.72), respectively. Five studies provided adequate information for the assessment of the discriminative ability of the EQ-5D-3L; four showed satisfactory discriminative ability of the index score to accurately distinguish patients based on the presence of apathy, dyskinesia, "wearing-off" period, and sweating disturbances.[64] The remaining study found the EQ-5D-3L was adequate in differentiating clinically different groups based on PD severity as well as various motor and non-motor symptoms; however, the discrimination was more evident for mild and severe cases of PD and less so for adjacent stages.[64]

The responsiveness of the EQ-5D-3L was reported in 12 studies in the aforementioned systematic review.[64] Six studies showed a statistically significant change in the EQ-5D index score over time, which was consistent with other established scales used as reference measures, including the UPDRS Part II, PDQ-39, PDQ-8, HY score, and Hospital Anxiety and Depression Scale (HADS). In the remaining six studies, the aforementioned measures did not show a consistent pattern of increase or decrease with the progression of disease.[64]

Minimal Clinically Important Difference

Information regarding an MCID for the EQ-5D among PD patients is scarce. The aforementioned systematic review reported an estimated MCID of 0.10 (range: 0.04 to 0.17) and 0.11 (range: 0.08 to 0.14) based on the UPDRS and PDQ-39 score, respectively; however, this was obtained from a conference abstract.[64] Other reported MCIDs for the EQ-5D-3L range from 0.03 to 0.07.[141]

Zarit Burden Interview

The ZBI is a commonly used, generic, self-reported measure to assess caregiver burden resulting from providing continuous and long-term physical, psychosocial, and financial support to patients with a disabling condition. The scale originated as a 29-item questionnaire but was later revised into a 22-item scale (ZBI-22), the same version used in study 001/002.[134] In addition, multiple shorter versions of ZBI are available, ranging from as short as one item to 18 items.[133] The 22-item scale is available in at least 47 languages, including English, French, German, Hindi, Japanese, Korean, Mandarin, Portuguese, Russian, and Spanish.[135] The ZBI-22 measures the perceived burden of caregivers for each of the 22 items on a 5-point Likert scale, ranging from 0 (never) to 4 (nearly always). Scores are then summed to create a total score that can range between 0 and 88, with higher scores indicating more burden.[132,133] The ZBI score is interpreted using the following cut-offs:

- 0 to 21 (little or no burden)
- 21 to 40 (mild to moderate burden)
- 41 to 60 (moderate to severe burden)
- 61 to 88 (severe burden).

Even though a number of studies examined the validity, reliability, and reference values of the ZBI-22 scale, only two cross-sectional studies involved caregivers of PD patients. However, neither used the English version. Hagell et al. assessed the psychometric properties of the Swedish version of the ZBI-22 among family caregivers of patients with PD.[131] Another multi-centre Spanish study conducted a validity assessment on several clinician and self-administered scales, including the ZBI-22.[35]

In both studies, the scaling assumptions were assessed from item-total correlations to determine the appropriateness of summing item scores into a total score. The item-total correlation ranged from 0.42 to 0.80 in the Swedish study[131] and 0.31 to 0.78 in the Spanish study,[35] indicating scaling assumptions were met for most items. Factor analysis identified five factors that accounted for 80% of the variance. These factors were the most important predictors of caregiver burden, including the psychological well-being of the caregivers themselves, clinical aspects of disease, patients' mood, and the HRQoL of patients and caregivers alike.[35] An assessment of targeting was done to determine how well the scale scores accord with the range of burden in the sample. Overall, a satisfactory targeting was found, as demonstrated by a floor/ceiling effect of < 2% and skewness ranging from 0.27 to 0.67.[35,131]

Internal consistency was satisfactory in both studies, with Cronbach's alpha 0.95 and 0.93 in the Swedish and Spanish studies, respectively.[35,131]

Construct validity was assessed in both studies. Hagell et al. reported moderate to strong correlations (range 0.36 to 0.69) between ZBI-22 and a number of scales and questionnaires for measuring similar aspects of health, including the SF-36 version 1, the sleep section of the Nottingham Health Survey, patients' PD duration, and the PD Activities of Daily Living Scale.[131] The Spanish multi-centre study also reported moderate to strong correlations between the ZBI-22 and the global and physical components of several HRQoL measures, including the Berthel index, CGI-S, EQ-5D, HY score, scales for outcomes in Parkinson disease-motor ADL, and the SF-36 ($0.25 < |r| < 0.60$), and relatively strong correlations with a number of mental health components of the SF-36 and HADS ($r > 0.60$).[35] Further validity was demonstrated after caregivers with a disease of their own reported an expectant higher ZBI-22 score than those without any concomitant disease, and caregivers' time and strain were associated with the scale.[35,131] Finally, the discriminative performance of ZBI-22 was assessed using AUROC curves, which represents the ability to accurately classify people with and without burden according to chosen cut-points. The 11 chosen cut-points for ZBI-22 showed a high discriminative ability, AUROC of 0.98, with a similarly high Youden index of 0.96.[131] ZBI-22 in the Spanish study also showed superior discriminative validity in accurately registering higher scores with advanced PD stages.[35]

Minimal Clinically Important Difference

No information on MCIDs for the ZBI-22 was found among caregivers of patients with PD.

Conclusion

- The PDHD was validated and found reliable in just a single study.
- The PDQ-39 is an MDS-recommended, self-administered, multi-dimensional, PD-specific HRQoL that has been thoroughly validated. Overall, internal consistency and test–retest reliability (inter- and intra-rater) were high. The construct and discriminant validity as well as responsiveness were relatively higher for domains measuring physical and functional aspects of PD compared with psychosocial symptoms.
- The CGI and its subscales have limited evidence of validity; no studies specifically validating CGI-I were found. The CGI-S showed high concordance with other clinician-administered instruments, but relatively lower concordance with patient-administered instruments. An MCID for CGI-I was also not found.
- The UPDRS and its four subscales have been validated extensively across different populations and are recommended by the MDS. The scale is easy to administer and had excellent inter-rater and intra-rater agreement when administered by different health professionals. Evidence of validity is satisfactory overall. Correlations between the UPDRS and a number of established measures of disability and functional impairment are high. However, some items in Part I are redundant or have suboptimal internal consistency, low sensitivity, and low specificity. Notably, validation metrics are not commonly measured in both “on” and “off” states and data from severe cases are disproportionately represented.
- The EQ-5D-3L is a well-validated measure of generic HRQoL that correlates strongly with physical attributes of standard measures of functional disabilities, but relatively weakly with psychosocial attributes. The scale showed varying responsiveness to clinical changes and limited sensitivity to detect changes in milder PD cases.
- The ZBI-22 has been validated for caregivers of patients with various conditions, including PD. Studies showed that scaling assumptions were generally met, discriminative validity was adequate, and internal consistency and correlations with the mental health components of established HRQoL measures were high; but correlations were moderate for the global and physical components of these measures. The physical and psychological well-being of caregivers, clinical severity of disease, patients’ and caregivers’ mood, and HRQoL all affected caregiver burden. No information was found regarding test–retest reliability, responsiveness, or MCID.

Appendix 6: Summary of Study 003 and Study 005

Objective

To summarize the results of the long-term safety extension studies 003 and 005, which evaluated the long-term safety, efficacy, and quality of life (QoL) in patients with advanced Parkinson disease (PD) receiving levodopa/carbidopa intestinal gel (LCIG) through percutaneous endoscopic gastrostomy with jejunal extension (PEG-J) tube.

Findings

Study Design

The study design characteristics of the multinational, multi-centre, open-label, long-term safety extension studies (Study 003 and Study 005) are summarized in Table 25. Patients who had participated in Study 001/002 and elected to continue after study completion — who also demonstrated a good response to immediate-release (IR) oral levodopa/carbidopa (OLC) or LCIG — were eligible for long-term safety extension Study 003 (N = 62). A "good response" was based on improvements on the Unified Parkinson's Disease Rating Scale (UPDRS), the 39-Item Parkinson's Disease Questionnaire (PDQ-39), or the Clinical Global Impression – Improvement scale (CGI-I). There was no minimum "off" time required at the beginning of the extension trial. The open-label extension was a continuation of study treatment that began immediately after the double-blind (DB) trial. Baseline was defined as the beginning of the long-term safety extension study, with baseline evaluations derived from the final measures of the DB trial. To maintain blinding from Study 001/002, all patients were hospitalized and re-titrated to the optimum LCIG dose for two to seven days, after which they continued on open-label LCIG infusion for the remainder of the 52 weeks. The LCIG infusion was taken continuously during the day (approximately 16 hours) and stopped at night, when all patients were permitted to take IR OLC if medically indicated. The starting dose of LCIG was based on the optimized OLC dose the patient received prior to randomization in the DB study, and could be adjusted by the investigator at any time based on the patient's medical condition. Patients were also permitted to taper off concomitant anti-PD medication any time after the LCIG treatment was initiated.

Patients who completed either Study 001/002 and its open-label safety extension (Study 003) or who completed Study 004 were eligible for enrolment in Study 005 (N = 262). Study 005 included patients from Australia, Canada, eastern Europe, Israel, New Zealand, the Russian Federation, Thailand, the US, and western Europe. Baseline was defined as the last assessment in the previous LCIG study. The LCIG infusion was administered in a manner similar to that in Study 003 (i.e., continuously during the day [approximately 16 hours] and cessation at night, when all patients were permitted to take IR OLC if medically indicated). The starting dose of LCIG was based on the optimized OLC dose the patient received in the prior open-label studies (i.e., Study 003 and Study 004), and could be adjusted by the investigator at any time based on the patient's medical condition. Study 005 is currently ongoing; therefore, the results presented in this report are based on interim analyses.

Table 25: Summary of the Design and Characteristics of Study 003 and Study 005

		Study 003	Study 005
DESIGNS & POPULATIONS	**Study design**	Open-label, multi-centre, multinational, long-term safety extension	
	Participants (N)	62	262
	Eligibility	Patients who elected to continue after completing the preceding 12-week study and demonstrated a good response to LC/IR or LCIG based on improvements on the UPDRS, PDQ-39, or CGI-I were eligible for enrolment.	Patients who completed either Study 001/002 and its open-label safety extension (Study 003) or who completed Study 004 were eligible for enrolment Patients with any medical, laboratory, psychiatric, or surgical issues deemed to be clinically significant and that could interfere with participation in the study by the investigator were excluded.
	Primary objective	To evaluate the long-term safety of LCIG	
	Secondary objective	To assess the long-term maintenance of efficacy and quality of life	
DRUGS	**Intervention**	LCIG as a homogenous suspension of levodopa (20mg/mL) and carbidopa monohydrate (5mg/mL) in an aqueous gel (sodium carboxymethyl cellulose) administered continuously (through the waking day, approximately 16 hours) through a portable infusion pump device with dosing based on the optimized levodopa/carbidopa dose that the patient received in prior study.	
	Comparators	NA	
DURATION	**Re-titration**	• 2 to 7 days • Patients were hospitalized to maintain blinding from Study 001/002 and re-titrated to the optimum LCIG dose	NA
	Treatment (open-label)	52 weeks (minus the duration of the re-titration period)	5-year follow-up
OUTCOMES	**Primary end point**	Frequency and severity of adverse events	Frequency of adverse events
	Other end points	Efficacy: • Change from baseline in “off” time • Change from baseline in “on” time without troublesome dyskinesia • Change from baseline in UPRDS total score (sum of parts I, II, and III) • Change from baseline in UPRDS scores individually: parts I, II, III, IV, and V • Change from baseline in the CGI-I HRQoL: • PDQ-39 • EQ-5D-3L • ZBI	Efficacy: • Change from baseline in “off” time • Change from baseline in “on” time without troublesome dyskinesia • Change from baseline in “on” time with troublesome dyskinesia • Change from baseline in UPRDS total score (sum of parts I, II, and III) • Change from baseline in UPRDS scores individually: parts II and III • Change from baseline in the CGI-I HRQoL: • PDQ-39

CGI-I = Clinical Global Impression – Improvement; EQ-5D-3L = EuroQol 5-Dimensions 3-Levels questionnaire; HRQoL = health-related quality of life; LCIG = levodopa/carbidopa intestinal gel; LC/IR = immediate-release oral levodopa/carbidopa; NA = not applicable; PD = Parkinson disease; PDQ-39 = 39-item Parkinson’s Disease Questionnaire; UPDRS = Unified Parkinson Disease Rating Scale; QoL = quality of life; ZBI = Zarit Burden Interview.

Source: Slevin et al. (2015),[142] Fernandez et al. (2018).[143]

Methods

The primary objective of Study 003 was to evaluate the long-term safety of LCIG based on the frequency and severity of treatment-emergent adverse events (TEAEs). TEAEs were defined as events that occurred on or after the first day of open-label treatment and no more than 30 days after PEG-J removal. The frequency of adverse events (AEs) was reported, including a summary of AEs by severity, those with an outcome of death, serious adverse events (SAEs), and those potentially related to study treatment (the drug and device). AEs that may have been related to LCIG initiation were evaluated by comparing the AEs reported during week 1 to week 4 for both treatment groups. Complications related to the infusion device were also monitored by safety assessments. Long-term maintenance of efficacy and QoL were evaluated as secondary end points. All patients who had a baseline and at least one post-baseline assessment of efficacy or QoL were included in the analyses of secondary end points. A one-sample t-test was used to assess within-group changes from baseline to each visit and end point.

Study visits in which safety was assessed through physical examinations that included stoma-site inspection, neurological examinations, vital sign and weight measurements, and excessive daytime sleepiness assessments were scheduled every six months in Study 005. AEs and product complaints could be reported at any time during the study and only those occurring during Study 005 were considered. Efficacy was assessed through the PD symptom diary, UPDRS, and the PDQ-39. All patients who received at least one infusion of LCIG were included in the safety population, whereas only the subset of patients enrolled in the US who had at least one efficacy assessment were included in the efficacy population. PD diary times were normalized to a 16-hour waking day and averaged for the three days prior to each study visit. A one-sample t-test was used to assess within-group changes from baseline to each visit and end point.

Patient Disposition

Patient disposition is summarized in Table 26. Patients who had previously received LCIG in the DB study (Study 001/002) were referred to as the “continuing-LCIG” group and patients who were previously treated with IR OLC were referred to as “LCIG-naive” in Study 003. A total of 62 of 71 patients (87%) randomized to the preceding DB trial proceeded to the open-label extension study (Study 003), of whom 33 were from the continuing-LCIG group and 29 were from the LCIG-naive group. A total of 55 patients (88.7%) completed the study, with 31 (93.9%) from the continuing-LCIG group and 24 (82.8%) from the LCIG-naive group. Patients from the continuing-LCIG group discontinued the intervention due to AEs (3.0%) and lack of efficacy (3.0%), whereas patients in the LCIG-naive group discontinued treatment due to AEs (6.9%) and withdrawal of consent (10.3%).

A total of 262 patients who completed either Study 003 or Study 004 were enrolled into Study 005. Among them, 110 (42%) completed the study and continued treatment with commercially available LCIG. Overall, 63 patients (24%) are still receiving ongoing treatment in Study 005. Eighty-nine patients (34%) discontinued Study 005, with the most common reason being AEs (24%).

Table 26: Patient Disposition in Study 003 and Study 005

Disposition, n (%)	Study 003			Study 005
	Continuing-LCIG	LCIG-Naive	Total	Total
Number of patients	33	29	62	262
Open-Label Treatment Phase				
Enrolled	33 (100)	29 (100)	62 (100)	262 (100)
Ongoing	NA	NA	NA	63 (24)
Completed	31 (93.9)	24 (82.8)	55 (88.7)	110 (42)
Discontinued	2 (6.1)	5 (17.2)	7 (11.3)	89 (34)
Adverse events	1 (3)	2 (6.9)	3 (4.8)	64 (24)
Withdrew consent	0 (0)	3 (10.3)	3 (4.8)	15 (6)
Lack of efficacy	1 (3)	0 (0)	1 (1.6)	7 (3)
Protocol violation	NR	NR	NR	2 (< 1)
Administrative	NR	NR	NR	1 (< 1)

LCIG = levodopa/carbidopa intestinal gel; NA = not applicable.

Source: Slevin, et al. (2015),[142] Fernandez et al. (2018).[143]

Baseline Characteristics

Study 003 and Study 005 baseline patient characteristics are summarized in Table 27.

Patients in Study 003 had a mean age of 64.1 (standard deviation [SD]: 7.9); 51.6% of the population was less than 65 years of age. The majority of the patients were male (70%) and 92% were white. The mean Mini-Mental State Examination (MMSE) total score among patients was 28.8 (1.5). Patients had lived an average of 10.7 (5.3) years with PD. The mean hours per day of “off” time, “on” time without troublesome dyskinesia, and “on” time with troublesome dyskinesia were 4.0 (2.5), 10.9 (2.8), and 1.1 (1.9), respectively. The mean UPDRS total score for patients was 28.2 (17.6); the mean CGI-S score was 3.3 (1.3); and the mean PDQ-39 summary index score was 26.7 (17.7). Patients in Study 005 had a mean age of 64.1 (SD: 8.9). The majority of the patients were male (52%), had lived an average of 11.4 (5.4) years with PD, and were treated with LCIG and IR OLC (81% at baseline; 92% at year 5).

Table 27: Baseline Characteristics in Study 003 and Study 005

Characteristics	Study 003			Study 005	
	Continuing-LCIG (N = 33)	LCIG-naive (N = 29)	Total (N = 62)	Safety Set (N = 262)	Efficacy Set (N = 86)
Age, Years					
Mean (SD)	63.6 (9.0)	64.8 (6.6)	64.1 (7.9)	64.1 (8.9)	65.1 (8.3)
Median (min, max)	NR	NR	NR	64 (39 to 84)	65 (41 to 82)
Age Category, n (%)					
< 65 y	19 (57.6)	13 (44.8)	32 (51.6)	NR	NR
≥ 65 y	14 (42.4)	16 (66.2)	30 (48.4)	NR	NR
Sex, n (%)					
Male	23 (70)	21 (72)	44 (71)	162 (62)	60 (70)
Race, n (%)					
American Indian or Alaska Native	1 (3)	0	1 (2)	NR	NR
Asian	1 (3)	3 (10.)	4 (7)	NR	NR
Black	0	0	0	NR	NR
White	31 (94)	26 (90)	57 (92)	NR	NR
Hispanic or Latino, n (%)	2 (6)	1 (3)	3 (5)	NR	NR
MMSE total score	28.8 (1.5)	28.9 (1.5)	28.8 (1.5)	NR	NR
Duration of Parkinson Disease, Years					
Mean (SD)	10.1 (4.8)	11.4 (5.7)	10.7 (5.3)	11.4 (5.4)	10.5 (4.5)
Median (min, max)	NR	NR	NR	10.4 (1.5 to 31.3)	9.6 (1.7 to 24.9)
"Off" time, hours per day	3.1 (2.6)	5.1 (2.0)	4.0 (2.5)	NR	NR
"On" time without troublesome dyskinesia, hours per day[a]	11.8 (2.7)	9.9 (2.6)	10.9 (2.8)	NR	NR
"On" time with troublesome dyskinesia, hours per day[b]	1.1 (2.0)	1.1 (1.7)	1.1 (1.9)	NR	NR
UPDRS total score (parts I, II, III)	26.4 (18.9)	30.3 (16.1)	28.2 (17.6)	NR	NR
CGI-S	3.0 (1.3)	3.7 (1.3)	3.3 (1.3)	NR	NR
PDQ-39 summary index	22.0 (17.1)	32.1 (17.2)	26.7 (17.7)	NR	NR

CGI-S = Clinical Global Impression – Severity of Illness; min = minimum; max = maximum; MMSE = Mini-Mental State Examination; NR = not reported; PDQ-39 = 39-item Parkinson's Disease Questionnaire; SD = standard deviation; UPDRS = Unified Parkinson's Disease Rating Scale.

Note: Data are means (SD) unless otherwise indicated.

[a] "On" time without troublesome dyskinesia equals "on" time without dyskinesia plus "on" time with non-troublesome dyskinesia.

Source: Slevin 2015,[142] Fernandez et al. (2018).[143]

Table 28: Concomitant Parkinson Disease Medications in Study 005

Concomitant PD Medication	Day 1 (N = 262)	Year 1 (N = 262)	Year 2 (N = 230)	Year 3 (N = 196)	Year 4 (N = 145)	Year 5 (N = 79)
LCIG and oral levodopa/carbidopa[a]	212 (81)	226 (86)	198 (86)	170 (87)	129 (89)	73 (92)
LCIG only	126 (48)	126 (48)	107 (47)	96 (49)	74 (51)	42 (53)
Concomitant PD medications	50 (19)	36 (14)	32 (14)	26 (13)	16 (11)	6 (8)

LCIG = levodopa/carbidopa intestinal gel; PD = Parkinson disease.

[a] Including patients who were on LCIG only without concomitant antiparkinsonian medications and patients who only took oral levodopa/carbidopa as concomitant anti-parkinsonian medication.

Source: Fernandez et al. (2018).[143]

Results

Safety

Detailed safety data in Study 003 and Study 005 are summarized in Table 29.

Nearly all (95%) patients experienced at least one AE in Study 003. AEs that were deemed "possibly or probably related to treatment" occurred in 77% of patients. The most frequently reported AE was incision-site erythema (29%), followed by falls (21%), decreased vitamin B6 (21%), and post-operative wound infection (18%). Notable harms reported by patients included: constipation (15%), insomnia (15%), nausea (15%), PD (13%), post-procedural discharge (13%), procedural pain (13%), dyskinesia (11%), freezing phenomenon (11%), and polyneuropathy (10%). The majority of the AEs were reported as mild to moderate in severity, although the data were not shown.

SAEs were reported in 23% of patients in Study 003 (15% in the continuing-LCIG group, 31% in the LCIG-naive group), the most common reason being complication of device insertion (5%) followed by abdominal pain (3%), asthenia (3%), and pneumonia (3%). Each of the following SAEs were reported in one patient (1.6%) and were also notable harms: gastrointestinal (GI) injury, peritonitis, hypertension, auditory hallucination, delusion, and hallucination. Further, the study reported complications related to the infusion device separately, and included complications related to the pump (55%), intestinal (J) tube (50%), PEG (36%), stoma site (44%), and other (16%), which were also notable harms. No deaths were reported in this study. Only three patients (5%) discontinued due to AEs.

Nearly all patients (94%) experienced at least one AE in Study 005. The most frequently reported AEs were fall (21%), decreased vitamin B6 (22%), urinary tract infection (19%), increase in blood homocysteine (18%) and decrease in weight (14%). Notable AEs reported by patients included: procedural-site reaction (13%), excessive granulation tissue (18%), incision-site erythema (15%), post-operative wound infection (23%), procedural pain (10%), abdominal pain (10%), constipation 29 (11%), nausea (12%), insomnia (11%), depression (11%), compulsive sexual behaviour (5%), pathological gambling (<1%), compulsive buying (1%), polyneuropathy (8%), PD (13%), and dyskinesia (10%).

SAEs were reported in approximately half (53%) of patients in Study 005, the most common reason being complication of device insertion (5%), pneumonia (6%), fall (5%), pneumonia aspiration (3%), post-operative wound infection (3%), and decreased weight (3%). A total of 62 patients (24%) discontinued the study; 38 were reported as deaths. Two of the deaths were considered to be possibly related to treatment with LCIG (intestinal dilatation and cardiac arrest).

Table 29: Adverse Events in Study 003 and Study 005

Harms, n (%)	Study 003			Study 005
	Continuing-LCIG (N = 33)	LCIG-naive (N = 29)	Total (N = 62)	Safety Set (N = 262)
Adverse Events	**31 (94)**	**28 (97)**	**59 (95)**	**NR (94)**
Fall	7 (21)	6 (21)	13 (21)	55 (21)
Decreased vitamin B6	8 (24)	5 (17)	13 (21)	58 (22)
Urinary tract infection	5 (15)	4 (14)	9 (15)	50 (19)
Seborrheic keratosis	5 (15)	3 (10)	8 (13)	NR
Arthralgia	5 (15)	2 (7)	7 (11)	NR
Blood homocysteine increased	5 (15)	2 (7)	7 (11)	48 (18)
Weight decreased	NR	NR	NR	36 (14)
SAEs Reported in ≥ 2% of Patients Across Groups	**5 (15)**	**9 (31)**	**14 (23)**	**NR (53)**
Complication of device insertion	1 (3)	2 (7)	3 (5)	14 (5)
Abdominal pain	1 (3)	1 (3)	2 (3)	NR
Asthenia	1 (3)	1(3)	2 (3)	NR
Pneumonia	0	2 (7)	2 (3)	17 (6)
GI hemorrhage	1 (3)	NR	NR	NR
Fall	NR	NR	NR	12 (5)
Pneumonia aspiration	NR	NR	NR	8 (3)
Post-operative wound infection	NR	NR	NR	8 (3)
Weight decreased	NR	NR	NR	8 (3)
Deaths				
Number of deaths	0	0	0	38 (15)
WDAE				
Number of discontinuations	NR	NR	3 (5)	62 (24)
Complications of device insertion	NR	NR	NR	5 (2)
Death of unknown cause	NR	NR	NR	5 (2)
Pneumonia	NR	NR	NR	4 (2)
Cardiac arrest	NR	NR	NR	3 (1)
Myocardial infarction	NR	NR	NR	3 (1)
Re-emergence of motor deficits	NR	NR	NR	3 (1)
Notable Harms[a]				
Device-Related Complications				
Pump complication	NR	NR	NR (55)	NR
Intestinal (J) tube complication	NR	NR	NR (50)	NR
PEG complication	NR	NR	NR (36)	NR
Stoma-site complication	NR	NR	NR (44)	NR
Complication of device insertion	NR	NR	NR	33 (13)
Device malfunction	NR	NR	NR	NR (85)
Device occlusions	NR	NR	NR	NR (57)
Device dislocation	NR	NR	NR	NR (56)
Other[b]	NR	NR	NR (16)	NR
Procedure- and Device-Associated AEs				
Procedural-site reaction	NR	NR	NR	33 (13)
Excessive granulation tissue	NR	NR	NR	41 (16)

Harms, n (%)	Study 003			Study 005
	Continuing-LCIG (N = 33)	LCIG-naive (N = 29)	Total (N = 62)	Safety Set (N = 262)
Incision-site erythema	7 (21)	11 (38)	18 (29)	38 (15)
Post-operative wound infection	5 (15)	6 (21)	11 (18)	59 (23)
Post-procedural discharge	3 (9)	5 (17)	8 (13)	NR
Procedural pain	4 (12)	4 (14)	8 (13)	27 (10)
GI AEs				
GI injury	1 (3)	NR	1 (2)	NR
Peritonitis	NR	1 (3)	1 (2)	NR
Abdominal pain	NR	NR	NR	27 (10)
Constipation	4 (12)	5 (17)	9 (15)	29 (11)
Nausea	4 (12)	5 (17)	9 (15)	32 (12)
Vascular Disorders				
Hypertension	NR	1 (3)	1 (2)	NR
Psychiatric Disorders				
Auditory hallucination	NR	1 (3)	1 (2)	NR
Delusion	NR	1 (3)	1 (2)	NR
Hallucination	NR	1 (3)	1 (2)	NR
Insomnia	2 (6)	7 (24)	9 (15)	29 (11)
Depression	NR	NR	NR	30 (11)
Compulsive sexual behaviour	NR	NR	NR	13 (5)
Pathological gambling	NR	NR	NR	1 (< 1)
Compulsive buying	NR	NR	NR	2 (1)
Polyneuropathy	3 (9)	3 (10)	6 (10)	22 (8)
Nervous System Disorders				
Parkinson disease	4 (12)	4 (14)	8 (13)	33 (13)
Dyskinesia	4 (12)	3 (10)	7 (11)	27 (10)
Freezing phenomenon	4 (12)	3 (10)	7 (11)	NR

AE = adverse event; GI = gastrointestinal; LCIG = levodopa/carbidopa intestinal gel; NR = not reported; TEAE = treatment-emergent adverse event; STEAE = serious treatment-emergent adverse event; WDAE = withdrawal due to adverse event.

[a] Reported as serious adverse events in Study 003.

[b] "Most of which were device connection issues."

Source: Slevin 2015,[142] Fernandez et al. (2018).[143]

Efficacy

The mean change from baseline of efficacy and QoL outcomes are summarized in Table 30. The mean amount of "off" time decreased in both the continuing-LCIG (–0.42; 95% CI, –1.39 to 0.54) and LCIG-naive groups (–2.34; 95% CI, –3.44 to –1.24) between baseline and week 52. The mean amount of "on" time without troublesome dyskinesia at week 52 increased from baseline in both groups as well (1.00 [95% CI, 0.07 to 1.93] and 2.19 [95% CI, 0.72 to 3.65] for the continuing-LCIG and LCIG-naive groups, respectively). A statistically significant change related to the UPDRS scores was not observed for either group, with the exception of the score for UPDRS Part IV (related to motor control) in the continuing-LCIG group. Lastly, an increase in the mean scores reported for the CGI-I at final assessment was statistically significant in both the continuing-LCIG and LCIG-naive groups.

QoL measurements were assessed in Study 003 as well, and are summarized in Table 30. The change in QoL from baseline for both groups — based on the PDQ-39, EQ-5D-3L, EQ-5D-3L visual analogue scale (VAS), and Zarit Burden Interview — was reported; however, none of the results were statistically significant.

Only the mean change from the Study 005 baseline to the Study 005 end point for the UPDRS total score (parts I, II, and III) and the individual scores for the UPDRS (parts II and III) as well as the PDQ-39 summary index score were reported in Study 005. Overall, no statistically significant changes were observed from baseline to last study visit.

Table 30: Efficacy Outcomes in Study 003 and Study 005

	Study 003				Study 005	
	N	Mean (SD) Change From Baseline	95% CI	*P* Value	N	Mean (SD) Change From Baseline
Efficacy Outcomes						
"Off" Time, h Per Day						
Continuing-LCIG	32	–0.42 (2.67)	(–1.39 to 0.54)	0.377	NR	NR[c]
LCIG-naive	27	–2.34 (2.78)	(–3.44 to –1.24)	< 0.001	NA	NA
"On" Time Without Troublesome Dyskinesia, h Per Day[a]						
Continuing-LCIG	32	1.00 (2.58)	(0.07 to 1.93)	0.036	NR	NR[c]
LCIG-naive	27	2.19 (3.70)	(0.72 to 3.65)	0.005	NA	NA
UPDRS Part I						
Continuing-LCIG	33	0.3 (1.9)	(–0.4 to 1.0)	0.361	NR	NR
LCIG-naive	26	0.7 (1.7)	(0.0 to 1.3)	0.06	NA	NA
UPDRS Part II						
Continuing-LCIG	33	0.5 (3.4)	(–0.7 to 1.7)	0.447	82	6.1 (5.5)
LCIG-naive	26	–1.0 (7.0)	(–3.9 to 1.8)	0.453	NA	NA
UPDRS Part III						
Continuing-LCIG	33	1.5 (7.0)	(–1.0 to 4.0)	0.226	82	9.3 (10.6)
LCIG-naive	25	–0.5 (10.4)	(–4.8 to 3.8)	0.82	NA	NA
UPDRS Total Score (Parts I, II, III)						
Continuing-LCIG	33	2.3 (9.0)	(–0.9 to 5.5)	0.16	82	16.9 (15.0)
LCIG-naive	25	–1.0 (15.0)	(–7.2 to 5.2)	0.748	NA	NA
UPDRS Part IV Dyskinesia Subscore (Sum of Questions 32, 33, 34)						
Continuing-LCIG	33	–0.8 (1.7)	(–1.4 to –0.3)	0.006	NR	NR
LCIG-naive	26	–0.1 (1.7)	(–0.8 to 0.6)	0.824	NA	NA
UPDRS Part IV						
Continuing-LCIG	33	–1.6 (2.5)	(–2.5 to –0.8)	< 0.001	NR	NR
LCIG-naive	26	–1.4 (3.0)	(–2.6 to –0.2)	0.022	NA	NA
CGI-I at Final Assessment[b]						
Continuing-LCIG	33	2.1 (1.2)	(1.7 to 2.5)	< 0.001	NR	NR
LCIG-naive	29	2.3 (1.6)	(1.7 to 2.9)	< 0.001	NA	NA
Quality of Life Outcomes						
PDQ-39 Summary Index						
Continuing-LCIG	32	1.5 (12.7)	(–3.1 to 6.1)	0.505	81	8.6 (13.3)
LCIG-naive	26	–3.5 (13.4)	(–8.9 to 1.9)	0.191	NA	NA

	Study 003				Study 005	
	N	Mean (SD) Change From Baseline	95% CI	*P* Value	N	Mean (SD) Change From Baseline
EQ-5D Summary Index						
Continuing-LCIG	33	–0.009 (0.173)	(–0.071 to 0.052)	0.755	NR	NR
LCIG-naive	26	–0.006 (0.220)	(–0.094 to 0.083)	0.898	NA	NA
EQ-5D Visual Analogue Scale						
Continuing-LCIG	33	–0.9 (15.1)	(–6.2 to 4.5)	0.74	NR	NR
LCIG-naive	26	4.5 (15.5)	(–1.8 to 10.8)	0.152	NA	NA
Zarit Burden Interview						
Continuing-LCIG	24	1.1 (9.7)	(–3.0 to 5.2)	0.576	NR	NR
LCIG-naive	20	–1.8 (9.0)	(–6.0 to 2.5)	0.397	NA	NA

CGI-I = Clinical Global Impression-Improvement scale; CI = confidence interval; EQ-5D = EuroQol 5-Dimensions questionnaire; h = hours; LCIG = levodopa/carbidopa intestinal gel; NA = not applicable; NR = not reported; PDQ-39 = 39-item Parkinson's Disease Questionnaire; SD = standard deviation; UPDRS = Unified Parkinson's Disease Rating Scale.

[a] "On" time without troublesome dyskinesia equals "on" time without dyskinesia plus "on" time with non-troublesome dyskinesia.

[b] For CGI-I, the *P* value is from a one-sample t-test comparing the mean CGI-I to 4 = no change. The CGI-I ratings are as follows: 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 =minimally worse, 6 =much worse, 7 = very much worse.

[c] Data were not provided for the mean change from the Study 005 baseline to the Study 005 end point; however, data were provided as the change from prior to LCIG infusion (in previous study) to the Study 005 end point (i.e., Study 001/002, Study 003, or Study 004 as baselines). Patients experienced approximately a 4-hour reduction in "off" time from prior to LCIG infusion to the Study 005 end point ($P < 0.001$). Patients also experienced approximately a 4-hour increase in "on" time without troublesome dyskinesia ($P < 0.001$) and a decrease of 0.6 hours in "on" time with troublesome dyskinesia ($P < 0.05$) from before LCIG infusion to the Study 005 end point. No significant change from the Study 005 baseline to the Study 005 end point were reported in any "off" or "on" time end points.

Source: Slevin 2015, [142] Fernandez et al. (2018).[143]

Limitations

There are several limitations to the long-term, open-label, non-randomized safety trials, Study 003 and Study 005. First, given that they were uncontrolled studies, it remains unclear whether the changes observed in their safety and efficacy profiles were due to a natural course of the disease or were attributed to long-term treatment with LCIG through a PEG-J tube. Open-label trial designs in which both the investigators and participants are not blinded to treatment allocation may have an impact on subjective outcomes, such as some of the patient-reported AEs, as well as on the outcomes related to efficacy and health-related QoL. Reporting of "off" and "on" time is also subjective; therefore, it is subject to bias. In addition, during Study 003 and Study 005, patients were able to continue concomitant anti-PD medication; this makes it difficult to ascertain the safety and efficacy of the intervention in isolation. The patients enrolled in these trials consisted of patients who elected to continue and who had demonstrated a good response to IR levodopa/carbidopa or LCIG based on improvements observed in the main study; therefore, the study population may be composed of patients who are more likely to tolerate and benefit from treatment with LCIG through a PEG-J tube compared with the general population of those living with PD. Also of note, data were incomplete for some outcomes, which may increase the potential for bias in the patient-reported outcomes if those with complete data had more favourable responses. Further, adjustments for multiple comparisons were not performed for the efficacy outcomes; thus, the risk of type I error is introduced.

Summary

In summary, Study 003 and Study 005 did not reveal any new signals regarding the safety of LCIG administered through a PEG-J tube for the treatment of advanced PD after up to 6.9 years of follow-up. Further, the long-term evaluation of the intervention efficacy demonstrated that the treatment effect was maintained throughout the trials. However, the interpretation of the safety and efficacy results is limited by the open-label nature of the study, the lack of a control group, and the lack of control for multiple statistical testing in addition to the use of subjective outcomes for most of the assessments. These limitations must be considered along with the interpretation of these results due to the uncertainty they introduce into the evaluation.

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