Long-term Safety and Efficacy of Levodopa-Carbidopa Intestinal Gel in Advanced Parkinson's Disease

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Word Count: 3,700 words (maximum 3,700 words)

Key Words: Parkinson's disease, levodopa-carbidopa intestinal gel, percutaneous endoscopic gastrojejunostomy, safety, infusion, clinical trial

Running Title: Long-term safety and efficacy of LCIG

Financial Disclosures/Conflicts of Interest Related to Publication/AbbVie: H.H.F. has received research support from and has served as consultant/scientific advisor and lecturer for AbbVie. J.T.B. has received research support from and has served as a consultant/scientific advisor for AbbVie. V.S.C.F. has received research support from AbbVie. M.F.L. has received research support from and has served as a consultant, advisor, and/or lecturer for AbbVie. R.L.R. has received research support from AbbVie and honoraria from AbbVie for an educational symposium. J.T.S. has received research support from and has served as an advisor for AbbVie. D.G.S. is an investigator in studies funded by AbbVie and has served as a consultant or received honoraria from AbbVie; honoraria paid by AbbVie were for activities unrelated to authorship. C.Z. has received educational grants from and has served as an advisor for AbbVie. A.D.V. has received compensation from AbbVie for consultancy and advisory board services. C.H., W.Z.R., M.F.F., and J.B. are employees of AbbVie, and hold AbbVie stock and/or stock options. K.C. and S.E. are former employees of AbbVie. A.J.E. has received compensation as a consultant/scientific advisory board member from AbbVie.

ABSTRACT:

Background: Levodopa-carbidopa intestinal gel (designated as carbidopa-levodopa enteral suspension in the United States) provides stable plasma levodopa concentrations and reduces motor fluctuations in advanced Parkinson's disease (PD) patients through continuous delivery of levodopa via percutaneous endoscopic gastrojejunostomy. We report long-term safety and efficacy outcomes from an open-label phase 3 treatment program.

Methods: PD patients (N=262) who completed a 12-week double-blind study and its 52-week open-label extension, or a separate 54-week open-label study, were enrolled in this ongoing, phase 3, open-label, multinational study (NCT00660673). Safety and efficacy assessments were collected every 6 months.

Results: The mean total duration of exposure to levodopa-carbidopa intestinal gel was 4.1 years (range: 1.2 to 6.9 years). The overall discontinuation rate was 34% (average annual discontinuation rate: 10%). Although most patients (94%) reported an adverse event, the rate of adverse events decreased over time; 53% experienced a serious adverse event. Of patients in this extension study, 54% required jejunal tube replacement during the study; 37% required percutaneous endoscopic gastrostomy tube replacement. Most patients were on levodopa monotherapy. Patients maintained reductions in "off" time and increases in mean "on" time without dyskinesia from initial LCIG infusion to study endpoint ($P<0.001$; n= 81). Activities of daily living and quality of life assessments demonstrated significant improvements that persisted through the study.

Conclusions: This long-term study demonstrates sustained and clinically meaningful benefits from levodopa-carbidopa intestinal gel in advanced PD patients. Although adverse event rates decreased over time, vigilance is required for device-related complications and adverse events.

Introduction

As Parkinson's disease (PD) progresses, nearly 90% of patients report disabling motor complications after 9 years of levodopa treatment,[1] including fluctuations between adequate treatment ("on" time) and poor mobility ("off" time).[2] These complications may be attributed to unstable levodopa plasma concentrations because of its short half-life, a narrowing therapeutic window, and erratic gastric emptying.[2-4] To overcome irregular levodopa concentrations after oral administration, levodopa-carbidopa intestinal gel (LCIG, designated in the United States as carbidopa-levodopa enteral suspension) continuously delivers levodopa via percutaneous endoscopic gastrojejunostomy (PEG-J). LCIG is used in PD patients who experience motor fluctuations not adequately controlled by oral dopaminergic medications. Pharmacokinetic studies demonstrate more consistent plasma levodopa concentrations with direct intestinal levodopa administration compared with oral formulations.[5,6]

Previous long-term LCIG safety and efficacy studies were limited by retrospective[7-9] or registry[10,11] study design, and small data sets.[12-14] Recently, larger randomized, controlled and open-label prospective studies demonstrated safety and efficacy of LCIG treatment through 1 year,[15-17] and safety was demonstrated for an average of 2 years in an open-label extension study.[18] LCIG treatment has consistently demonstrated significant reductions in "off" time and improvements in "on" time without increasing troublesome dyskinesia.[15-17] We report our findings on patients previously enrolled in phase 3 LCIG studies[15-17] who were allowed continued access to LCIG treatment through this open-label study until treatment became commercially available in each patient's home country. This is the longest prospective multinational study that presents LCIG safety and efficacy for advanced PD patients, with a mean follow-up of 4.1 years.

Methods

Study Design and Treatment

Advanced PD patients with motor fluctuations not adequately controlled by oral dopaminergic medications, who completed either a 12-week double-blind study[16] (NCT00660387/NCT0357994) and its 52-week open-label extension[17] (NCT00360568), or a separate 54-week open-label study[15] (NCT00335153), were eligible for enrollment in this ongoing, phase 3, open-label, multinational study (NCT00660673). Enrollment began in November 2009 and was completed in October 2012. Patients could remain in the study until they were transitioned to a locally available commercial product. Patients were enrolled from Australia, Canada, Czech Republic, Israel, New Zealand, Poland, Portugal, the Russian Federation, Thailand, the United Kingdom, and the United States. Patients were excluded if they had any medical, laboratory, psychiatric, or surgical issues deemed by the investigator to be clinically significant and which could interfere with the patient's participation in the study.

Patients received LCIG continuously administered through PEG-J tubing directly into the jejunum via a portable pump for 16 hours/day. Patients' initial LCIG dose was the same as that received at the end of their previous open-label LCIG study. Subsequent dose adjustments were made by the investigator as clinically indicated. In addition to a morning dose (to prime the intestinal tube and rapidly achieve the therapeutic dose) and the continuous infusion, patients could self-administer additional doses of LCIG to address immediate subjective needs (eg, motor function deterioration). Patients could use oral levodopa-carbidopa only for scheduled or supplemental bedtime/overnight doses after the pump was disconnected for the night.

This study was conducted in accordance with the Good Clinical Practice Guideline as defined by the International Council on Harmonization, The Declaration of Helsinki, and all applicable federal and local regulations and institutional review boards.

Assessments

Safety Assessment

Patients had scheduled study visits every 6 months. Subjects transitioning to commercial product had a final study visit. Subjects discontinuing LCIG had their PEG-J removed and a final follow-up 1 week later. At each study visit, safety was assessed via physical examinations that included stoma site inspection, neurological examinations, vital sign and weight measurements, and excessive daytime sleepiness assessments. Laboratory tests to evaluate selective B vitamin deficiencies were added in Protocol Amendment 2 (July 2011); because some patients were already enrolled at that time, not all patients had vitamin levels assessed. Impulsive behavior was assessed using the Minnesota Impulsive Disorders Interview (MIDI). Annually, the PEG-J was evaluated by a gastroenterologist. An electrocardiogram and clinical laboratory tests were performed at the final study visit. Use of vitamin supplementation was made at the investigator's discretion, regardless of laboratory values. Adverse events (AEs) and product complaints could be reported at any time during the study.

Efficacy Assessment

Protocol amendment 4 (December 2013) for the extension study added the following efficacy assessments that had been used in the qualifying studies for patients at US sites: the PD symptom diary[19,20] (PD diary), Unified Parkinson's Disease Rating Scale (UPDRS) and the Parkinson's Disease Questionnaire-39 (PDQ-39).

Statistical Analysis

All patients who received at least one infusion of LCIG in the current study were included in the safety population. The subset of patients who were enrolled in the United States and had at least one efficacy assessment in the current study were included in the efficacy population. The last assessment in the previous LCIG study served as baseline for the current study. The change in efficacy measures from baseline in the current study as well as from the time of each patient's initial LCIG infusion in one of the previous studies was evaluated.

AEs were coded using the *Medical Dictionary for Regulatory Activities* (MedDRA, version 14.0). AEs could be coded to more than one preferred term. For example, AEs coded to "complication of device insertion" could also be coded to one or more term descriptive of the event (eg, "abdominal pain", "duodenal ulcer", "abdominal discomfort", or "bezoar"). This manuscript includes only new AEs reported in this long-term, open-label study. Standardized search strategies based on MedDRA preferred terms identified AEs of special interest in the following categories: weight loss, polyneuropathy, and procedure/device-associated events. The polyneuropathy-related search included preferred terms in either the Peripheral Neuropathy or Guillain-Barre Syndrome standardized MedDRA query (narrow search), such as polyneuropathy, decreased vibratory sense, peripheral neuropathy, peripheral sensory neuropathy, neuralgia, demyelinating polyneuropathy, and sensory disturbance.

Efficacy variables based on the PD diary included "off" time, "on" time without troublesome dyskinesia, and "on" time with troublesome dyskinesia. "On" time without troublesome dyskinesia included "on" time without dyskinesia as well as "on" time with non-troublesome dyskinesia. 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 paired *t* test assessed significance in change of

efficacy measures. Data are presented through the 30 September 2015 cutoff date.

Results

Patients

A total of 262 patients from 11 countries participated in this open-label extension study and contributed data for the safety dataset (Fig. 1). Most patients were male (62%), and 43% were from the United States (Table 1). Only patients from the United States (n=86) were included in the efficacy subset. These patients had similar baseline characteristics to the overall safety population. As of the cutoff date, 110 patients (42%) had completed the study and were transitioned to commercially available LCIG; 89 (34%) had prematurely discontinued LCIG for any reason, including AE (24%), lack of efficacy (3%), withdrawn consent (6%), administrative reasons (< 1%), and protocol violations (< 1%). As of the cut-off date, 63 patients (24%) were still participating in the study because they lived in countries where LCIG was not yet commercially available.

The mean total exposure to LCIG in this extension study and previous study was 4.1 years (median: 4.3 years; range: 1.2 to 6.9 years). A total of 196 patients (75%) were exposed for at least 2 years in this study (plus 1 year in the preceding studies); overall treatment with LCIG was 1081 patient-years with 800 patient-years in this extension study. The average overall discontinuation rate was 10%/year. For the efficacy population, the mean (standard deviation [SD]) total daily dose of levodopa was 1588 (651) mg at study baseline (n=71) and 1783 (768) mg at study endpoint. During the study, most patients (ranging from 86% in year 1 to 92% in year 5) were on levodopa-carbidopa monotherapy (LCIG and oral levodopa-carbidopa), with half (ranging from 47% to 53%) not taking any other PD medications in addition to LCIG (Supplemental Table 1). At data cutoff, 30 of 71 patients used an extra LCIG dose (average of 141 mg/day).

Safety

Adverse Events

Most patients (94%) had an AE during the study; the most frequently reported AEs are shown in Table 2. Events reported as "postoperative" as well as the term "complication of device insertion" were not always temporally linked to the procedure; "postoperative" was not defined with a specific length of time and referred to an event (eg, wound infection) that occurred any time after the procedure. The number of patients with one or more AEs declined over time (year 1: 79%; year 2: 78%; year 3: 69%; year 4: 61%; year 5: 48%). Events associated with the procedure/device included postoperative wound infection, excessive granulation tissue, incision site erythema, complication of device insertion, procedural site reaction, abdominal pain, and procedural pain; the prevalence of these events decreased over time (Fig. 2a). Half (53%) of the safety population experienced a serious AE; the most common serious AEs are shown in Table 2. Patients experienced minimal changes in orthostatic blood pressure during the study (mean [SD] change from baseline: systolic, 0.2 [17.9] mmHg; diastolic, -0.2 [13.4] mmHg).

Discontinuations Due to Adverse Events

AEs led to discontinuations in 62 patients (24%), including 38 (15%) deaths. Of AEs leading to discontinuation, 14 patients (5%) discontinued because of a procedure/device-related AE. The most common AEs leading to discontinuation were complication of device insertion (n=5, 2%), death of unknown causes (n=5, 2%), pneumonia (n=4, 2%), cardiac arrest (n=3, 1%), myocardial infarction (n=3, 1%), and reemergence of motor deficits often due to interruption in drug delivery (n=3, 1%).

Weight Loss

The mean (SD) change from baseline in weight was a loss of 3.96 (6.68) kg (range: a loss of 30.7 kg to a gain of 12.3 kg). Less than half (48.4%) of patients experienced weight loss greater than 7%. Weight loss was reported as an AE at the investigator's discretion. Weight loss–related AE terms including weight decreased, dysphagia, decreased appetite, hypophagia, and malnutrition were reported in 47 patients (18%); 36 patients (14%) reporting weight decreased. Weight loss was considered serious in 10 (3.8%) patients (8 weight decreased and 1 each of dysphagia and malnutrition); only one case (dysphagia) led to discontinuation.

Polyneuropathy

Polyneuropathy-related symptoms were reported in 22 patients (8%). One polyneuropathy event was considered serious. None of these polyneuropathy-related events led to study discontinuation. During the current study, polyneuropathy-related AE rates were relatively constant (year 1: 2.3%; year 2: 3.0%; year 3: 3.0%; year 4: 1.9%; year 5: 1.2%).

Mean laboratory values for vitamin B6, vitamin B12, folic acid, and methylmalonic acid were in normal ranges for all patients with recorded laboratory values; mean homocysteine levels were higher than the normal range (Supplemental Table 2). Of the 22 patients who experienced polyneuropathy-related AEs, mean laboratory values were in normal ranges, except for homocysteine. The percentage of patients with polyneuropathy who had laboratory values above or below the normal ranges was like rates seen in the overall population. Nineteen of the 22 patients with polyneuropathy-related events were on vitamin supplementation. Of the 22 patients who experienced a polyneuropathy AE, only one patient experienced such an AE in their previous LCIG study. This patient reported polyneuropathy and sensory disturbance on day 309 after LCIG initiation; vitamin levels were not collected at that time.

Impulsive and Compulsive Behaviors

Impulse control behaviors reported based on the MIDI were (n [%] patients at study baseline and study endpoint, respectively): pathological gambling (1 [0.4%] and 1 [0.4%]), compulsive buying (1 [0.4%] and 2 [0.8%]), and compulsive sexual behavior (1 [0.4%] and 13 [5.1%]).

Device Complaints and Tube Replacements

Device complaints (ie, related to pump and tube complaints, but not necessarily associated with an AE) occurred in 244 patients (93%); the most common device complaints included device malfunction (85%), device occlusion (57%), and device dislocation (56%). Of note, device malfunction could be double-coded to other complaints, including device occlusion and device dislocation. The number of patients with device complaints associated with AEs generally decreased over time (Fig. 2b). Of the 244 patients with device complaints, 80% had their pump replaced. The number of patients with one or more device complaint(s) generally decreased over time (Supplemental Fig. 1). Overall, 167 patients (63.7%) had one or more device complaint(s) that resulted in either PEG or J tube replacement (average of 29.3% per year, range: 25.3% to 32.7%).

More than half (n=146, 56%) of patients did not require PEG tube replacement; 86 (33%) had one PEG tube replacement and 30 (11%) had more than one PEG tube replacement (Supplemental Fig. 2a). Approximately one-third (n=88, 34%) of the patients did not require J tube replacement, 69 (26%) had one J tube replacement, and 105 (40%) had more than one J tube replacement. The average (SD) PEG tube duration was 790.2 (438.1) days (range: 55 to 1941 days); the average (SD) J tube duration was 575.2 (399.1) days (range 55 to 1941 days). PEG and J tube replacements occurred at a relatively constant rate during this multiyear study

(Supplemental Fig. 2b). The average annual rate of PEG and J tube replacements was 15.7%

and 30.2%, respectively.

Deaths

There were 38 deaths (15%), of which two (intestinal dilatation and cardiac arrest) were

considered by the investigator to be possibly related to treatment (described in detail

previously[18]). The remaining 36 deaths were deemed unrelated to treatment and were mostly

caused by complications of disease progression and advancing age.

Efficacy

Patients in the efficacy cohort (US patients only) experienced a significant decrease of nearly

4 hours in mean daily hours of "off" time from prior to initial LCIG infusion to study endpoint

($P < .001$), with no significant change from study baseline to endpoint (Fig. 3a). Patients also

experienced a significant increase of approximately 4 hours in mean daily hours of "on" time

without troublesome dyskinesia ($P < .001$; Fig. 3b) that was maintained. Patients' mean daily

"on" time with troublesome dyskinesia was significantly lower (decrease of 0.6 hours) from prior

to initial LCIG infusion to study baseline ($P < .05$; Fig. 3c); however, this reduction was not

maintained during the extension study.

UPDRS total score, as well as part II (activities of daily living) and part III (motor) scores,

demonstrated significant improvements (mean score improvements of 3.03 and 4.77,

respectively) from prior to initial LCIG infusion to study baseline, that persisted through the

remainder of the study (Supplemental Table 3). Similarly, PDQ-39 summary index scores

demonstrated a mean improvement of 8.1 from prior to initial LCIG infusion to study baseline

that persisted through study endpoint.

Discussion

This study includes follow-up of patients who initiated LCIG treatment in a previous randomized controlled trial and an open-label trial, thus our findings are limited by differences in study designs and selection biases of the original studies from which patients were recruited. Patients were recruited from specialized movement disorders centers and therefore may be managed differently than patients in typical hospital settings. Efficacy was only assessed in a subset of the population in an open-label setting, which may overestimate the true benefit of LCIG beyond that reported in the parent studies. The study-required AE reporting may be artificially inflated; however, patient-monitoring in this study is closer to clinical practice than the preceding studies with visits every 6 months and limited study-specific assessments. Despite these limitations, this is the longest prospective study to date evaluating safety and efficacy of LCIG, with an average infusion of 4.1 years (median: 4.3 years; range: 1.2 to 6.9 years). Although a high incidence of AEs was noted, long-term use was associated with a relatively low[21] annual discontinuation rate (average: 10% per year) with overall discontinuation rates similar to other long-term follow-up studies[8-10,13,21-28] and low incidence of serious AEs.

The most frequently reported AEs were associated with PEG-J complications (mainly related to stoma site maintenance), comorbidities associated with advanced PD (eg, fall, fracture), aging (eg, fractures, osteoarthritis), or dopaminergic therapy (eg, dyskinesia, insomnia). The overall safety profile was like that reported in a recent integrated summary of safety of an average LCIG exposure of just over 2 years,[18] as well as prospective open-label[10,11,13,25-29] and retrospective observational studies.[7-9,14,22,23] A total of 36 (14%) patients reported AEs related to weight loss, as was also reported in the integrated safety study (59 patients, 14%),[18] and was similar to rates reported in a retrospective survey of over 900 patients,[23] and a prospective

open-label routine-care study of 59 patients.[11] Although impulse control disorders are common

in PD patients, and were an exclusion to enrollment, the treatment-emergent rate in this study

was low, with an increase in compulsive sexual behavior from study baseline to the end of the

study from 0.4% to 5.1%. Increased rates of impulse control disorders from study baseline to

endpoint is not uncommon—a study assessing long-term rotigotine treatment identified a

frequency of impulse control disorders of 0.6% after 6 months that increased to 9% after 6.5

years.[30]

Nonambulatory patients with enteral tubes for nutrition have experienced an average J tube

longevity of 3 to 6 months[31]; PD patients treated with LCIG are mobile and issues related to

enteral tube longevity (eg, tube displacement), would be expected. However, the PEG and J

tubes were durable during LCIG treatment, with an average PEG and J tube duration of 2.2

years and 1.6 years, respectively. The average tube longevity in this study is greater than the

average longevity of 12 months reported in a retrospective survey[23] and was like the 2.4-year

average longevity reported in an observational study.[24] Generally, PEG and J tubes are

replaced when needed; however, it is unknown how many tubes were replaced preventively, as

a cosmetic measure (eg, deterioration in the tube appearance), or whether the PEG and J

components were replaced independently. In addition, J tubes require replacement when PEG

tubes are replaced. PEG and J tubes were each replaced a median one time in the study;

patients with an unusual number of tube replacements (ie, more than five) generally had unique

circumstances. For example, one patient with 12 J tube replacements had dementia and

frequently pulled the tube out during confusional states. Other studies have cited increased

dementia (which results in accidental removal of tubes) as a reason for discontinuation,[28] and is

a point of consideration when deciding if a patient should continue LCIG treatment. Patients

who had device complaints commonly had their pump replaced to correct situations such as error codes.

The polyneuropathy rate in this population (3.4%) is similar to what has been reported in observational studies of patients treated with LCIG (rates of 3% reported in 2 studies,[10,29] 5.4%,[27] and 7%[11]); polyneuropathy rates were similar in the previous study (first year of treatment), with 18 patients (4.4%) experiencing polyneuropathy.[15] Similarly, 33 patients (8.0%) experienced polyneuropathy-related events in the first year of treatment (previous study)[15] and 22 (8%) reported polyneuropathy-related symptoms in the current study, thus indicating a relatively constant rate of polyneuropathy and polyneuropathy-related events. These rates are much lower than the polyneuropathy rates of 14%,[13] 19%,[32] and 35%[25] reported in other prospective open-label studies. Despite reports that polyneuropathy with levodopa treatment may be associated with hyperhomocysteinemia and low levels of vitamin B6, vitamin B12, folic acid, and methylmalonic acid,[33] patients experiencing polyneuropathy-related AEs in this study had mean laboratory values for these vitamins (except homocysteine) that were in normal ranges. However, most patients experiencing polyneuropathy-related AEs were on some level of vitamin supplementation. In addition, vitamin levels were not assessed after fasting. As a result, causality between LCIG, vitamin deficiencies, and polyneuropathy, cannot be established. Monitoring these vitamin levels was included as an amendment to the protocol for this study, thus baseline vitamin levels (before initial LCIG treatment in previous studies) were not available for most patients. Further systematic surveillance of vitamin levels is warranted to determine if vitamin supplementation may be considered in these patients.

Motor improvement from LCIG treatment was sustained and clinically meaningful as demonstrated by decreased "off" time, and increased "on" time without troublesome dyskinesia.

Although these motor improvements were not supported by the UPDRS Part II scores and

PDQ-39 summary index and subdomain scores, there was no motor worsening, as indicated by

negligible change in the "on" state UPDRS Part III scores. Diminished improvement over time in

PDQ-39 scores has been reported in long-term follow-up of patients treated with deep brain

stimulation, which may reflect disease progression, treatment-related AEs (such as speech

deterioration[34]), related comorbidities, or emergence of treatment-resistant symptoms.[35]

Because of general disease progression, advanced PD patients typically experience increases

in UPDRS Part II scores; levodopa-treated patients have experienced PD progression in the

form of an increase of 1.72 points/year in UPDRS Part II[36] (compared with an increase of 4.4

points/year in untreated patients[37]). In the current study, patients experienced an approximate

rate of increase of 1.5 points/year. Further, these results are similar to other long-term open-

label studies, which reported slight increases in UPDRS Part II scores after 24 months of

treatment,[27] and no change in UPDRS Part II scores after 4 years.[10] A retrospective study that

compared outcomes in patients receiving LCIG, deep brain stimulation, or optimized standard

oral therapy found that after an average of 5 years of treatment, the magnitude of worsening of

UPDRS Part II scores was similar between patients receiving LCIG and deep brain stimulation

and was lower for those patients receiving optimized oral therapy, indicating that LCIG and deep

brain stimulation ameliorated the deterioration of activities of daily living that occurs in patients

treated with optimized oral medication.[14]

In the initial 64 weeks of LCIG treatment in previous studies, the most common AEs were

related to the procedure;[15,16] however, with long-term use, patients experienced fewer of these

complications. Most patients were on levodopa monotherapy, and their levodopa dose was

constant or slightly increased over time, suggesting long-term tolerability of the dose needed to

control motor symptoms/fluctuations. No correlation was noted between peripheral neuropathy

and vitamin B levels, other than high homocysteine. Despite sustained motor improvements provided by LCIG in this advanced PD population, several comorbidities and complications, including death, do occur. Device-related complications were common and required vigilance, although they were generally reversible and seldom led to discontinuation. AEs were typical of the known risks of the PEG-J system, the advanced disease state, or the patient population. Therefore, despite the seemingly high rate of AEs, our long-term study suggested an overall favorable benefit/risk profile for long-term LCIG treatment.

V.S.C.F. receives a salary from NSW Health, has received research grants from the National

Health and Medical Research Council of Australia and AbbVie, and is on Advisory Boards

and/or has received travel grants from AbbVie, Allergan, Hospira, Ipsen, Lundbeck, Merz

Pharmaceuticals, Mundi Pharma, and UCB.

M.F.L. has served as a consultant, advisor, and/or lecturer for Teva, US World Meds, Merz

Pharmaceuticals, UCB, AbbVie, Acadia, Auspex, Lundbeck, Cynapsus, USWM, and Impax, and

has received research support from NIH, AbbVie, Parkinson's Study Group, USWM, the Michael

J. Fox Foundation for Parkinson Research, Synosia Pharmaceuticals, Merz Pharmaceuticals,

Ipsen, Pharma Two B, Civitas, Biotie, and Cynapsus.

R.L.R. has no owner interest in any pharmaceutical company but has received research support

from AbbVie, Allergan, Auspex, Biotie Therapeutics, Dystonia Coalition, Huntington Study

Group, Ipsen, Merz Pharmaceuticals, National Parkinson Foundation, NIH/NINDS, Parkinson's

Study Group, and Chelsea. He has also received honoraria from PeerView Institute for

Medication Education, Merz Pharmaceuticals, Lundbeck, Chelsea, and the CME Meeting, and

honoraria from AbbVie for an educational symposium.

J.T.S. has served as an advisor for AbbVie and Cynapsus Therapeutics Inc. He has also served

as a speaker for Teva and AbbVie, and has received research support from AbbVie, Biotie, NIH,

Parkinson Study Group, and the Veterans Administration.

D.G.S. is a member of the faculty of the University of Alabama at Birmingham and is supported

by endowment and University funds. Dr. Standaert is an investigator in studies funded by

Abbvie, Inc., the American Parkinson Disease Association, the Michael J. Fox Foundation for

Parkinson Research, Alabama Department of Commerce, and NIH grants P01NS087997, P20NS087997, R25NS079188, P2CHD086851, and P30NS047466. He has a clinical practice and is compensated for these activities through the University of Alabama Health Services Foundation. In addition, since January 1, 2016 he has served as a consultant for or received honoraria from, Serina Therapeutics, Abbvie (honoraria paid by AbbVie were for activities unrelated to authorship), Voyager Therapeutics, the Michael J. Fox Foundation for Parkinson Research, The International Parkinson Disease and Movement Disorder Society, the National Institutes of Health, The American Institute for Biological Sciences, Rush University, Huntsville Hospital, UCSD, Voyager Therapeutics, and he has received royalties for publications from McGraw Hill, Inc.

C.Z. has served as an advisor for AbbVie, Teva, Cynapsus, Lundbeck, UCG, and Merz Pharmaceuticals, and has received honoraria from Teva, UCB, US World Meds, Cynapsus, AbbVie, Acadia, Lundbeck, and Merz Pharmaceuticals; honoraria paid by AbbVie were for activities unrelated to authorship. She has received educational grants from AbbVie, Teva, and Allergan.

A.D.V. has received compensation from AbbVie for consultancy and advisory board services. He has also received compensation for consultancy services from CVS/Caremark Pharmacy and Therapeutics Committee.

C.H., W.Z.R., M.F.F., and J.B. are employees of AbbVie, and hold AbbVie stock and/or stock options.

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Author Roles

Specific roles in the project and manuscript preparation shown below are defined as follows:

1. Research project: A. Conception, B. Organization, C. Execution

2. Statistical analysis: A. Design, B. Execution, C. Review and Critique

3. Manuscript preparation: A. Writing of the first draft, B. Review and critique

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W.Z.R.: 1A, 1B, 2A, 2B, 2C, 3A, 3B
J.B.: 1A, 1B, 2C, 3A, 3B
A.J.E.: 1B, 1C, 2C, 3A, 3B

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TABLE 1. Demographics and baseline disease characteristics

Characteristic, n (%)	Safety population N = 262	Efficacy population[a] n = 86
Age (years) mean (SD)	64.1 (8.9)	65.1 (8.3)
Median (range)	64 (39 – 84)	65 (41 – 82)
Sex, n (%)		
Male	162 (62)	60 (70)
Female	100 (38)	26 (30)
Country, n (%)		
United States	113 (43)	86 (100)
Russian Federation	43 (16)	
Czech Republic	22 (8)	
Portugal	14 (5)	
Thailand	13 (5)	
Australia	12 (5)	
Canada	11 (4)	
United Kingdom	11 (4)	
New Zealand	10 (4)	
Israel	9 (3)	
Poland	4 (2)	
Mean (SD) weight, kg	69.8 (15.3)	74.2 (15.2)
Median (range)	68.3 (40.0 – 121.4)	70.68 (47.3 – 121.4)
Mean (SD) BMI, kg/m^2	24.2 (4.2)[b]	25.0 (4.7)
Median (range)	23.6 (16.4 – 37.3)[b]	23.9 (17.6 – 37.3)
Mean (SD) orthostatic systolic blood pressure[c], mmHg	-7.1 (13.8)	-9.9 (14.2)
Median (range)	-5.0 (-59.0 – 25.0)	-8.0 (-56.0 – 17.0)
Mean (SD) orthostatic diastolic blood pressure[c], mmHg	-1.7 (10.1)	-1.9 (10.3)
Median (range)	-0.5 (-66.0 – 41.0)	0 (-46.0 – 20.0)
Mean (SD) duration of Parkinson's disease, years	11.4 (5.4)	10.5 (4.5)
Median (range)	10.4 (1.5 – 31.3)	9.6 (1.7 – 24.9)

SD, standard deviation; BMI, body mass index.

[a]Per protocol amendment, patients in the efficacy population were only from the United States.

[b]n = 259.

[c]Change from sitting to standing position.

TABLE 2. Adverse events (AEs) and serious AEs

Parameter[a,b]	N = 262 n (%)
AEs Occurring in ≥ 10% of Patients	
Postoperative wound infection	*59 (23)*
Vitamin B6 decreased	58 (22)
Fall	55 (21)
Urinary tract infection	50 (19)
Blood homocysteine increased	48 (18)
Excessive granulation tissue	*41 (16)*
Incision site erythema	*38 (15)*
Weight decreased	36 (14)
Complication of device insertion[c]	*33 (13)*
Parkinson's disease[d]	33 (13)
Procedural site reaction	*33 (13)*
Nausea	32 (12)
Depression	30 (11)
Constipation	29 (11)
Insomnia	29 (11)
Abdominal pain	*27 (10)*
Dyskinesia	27 (10)
Procedural pain	*27 (10)*
Serious AEs Occurring in ≥ 3% of Patients	
Pneumonia	17 (6)
Complication of device insertion[c]	*14 (5)*
Fall	12 (5)

Pneumonia aspiration	8 (3)
Postoperative wound infection	*8 (3)*
Weight decreased	8 (3)

[a]A single event could be coded to ≥ 1 MedDRA preferred term descriptive of the event.

[b]Events associated with the procedure or device are italicized.

[c]Events with this term were most often additionally coded to "abdominal pain", "duodenal ulcer", "abdominal discomfort", or "bezoar".

[d]Refers to the reemergence of Parkinson's symptoms, often due to a problem with drug delivery.

FIGURE LEGENDS

FIG. 1. Disposition of patients. IR-LC, immediate-release oral levodopa-carbidopa;

LCIG, levodopa-carbidopa intestinal gel.

FIG. 2. (a) Prevalence of AEs related to the procedure or device are reported for those AEs

occurring in ≥ 5% of patients in any year of the study and (b) patients with ≥ 1 device complaint

associated with an AE over 5 years. AE, adverse event.

FIG. 3. Mean daily hours of (a) "off" time, (b) "on" time without troublesome dyskinesia, and (c)

"on" time with troublesome dyskinesia in US patients (n = 81) from the first LCIG study dose

through the continued-access-to-treatment study. "Prior to initial LCIG infusion" occurred in a

previous study, before the first LCIG infusion, and a portion of these patients (n = 19) were

administered immediate-release levodopa-carbidopa for 12 weeks during the double-blind study

prior to their first LCIG infusion in the following 52-week open-label extension study. "Study

Baseline" refers to the last assessment in a previous study, which served as a baseline for this

open-label extension study; "Endpoint" refers to measurements at the cutoff date for this open-

label, extension study. Error bars indicate standard deviation. **$P < 0.001$; *$P < 0.05$.

LCIG, levodopa-carbidopa intestinal gel; TSD, troublesome dyskinesia.
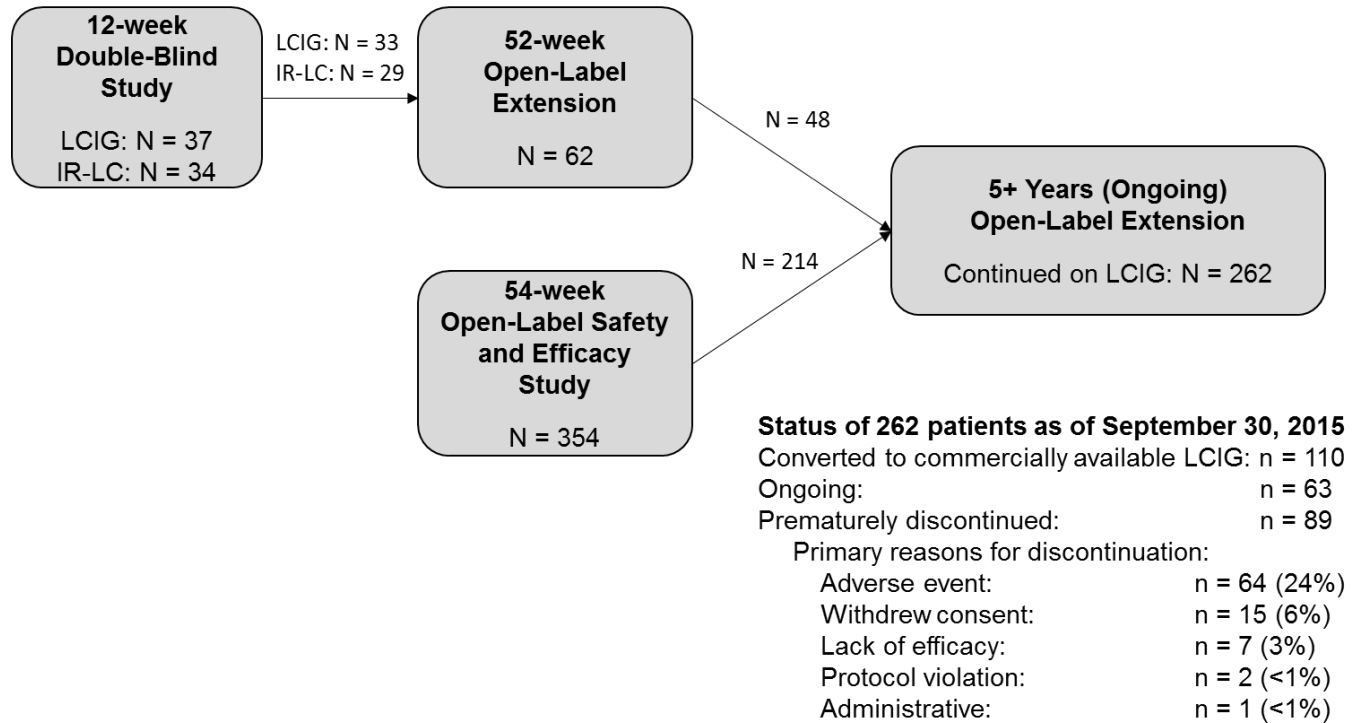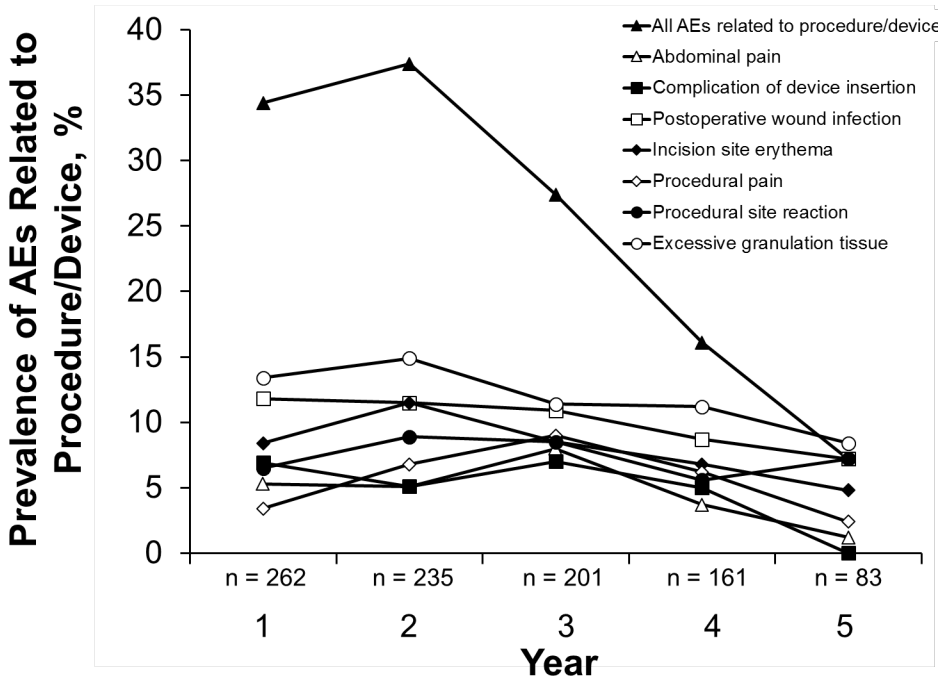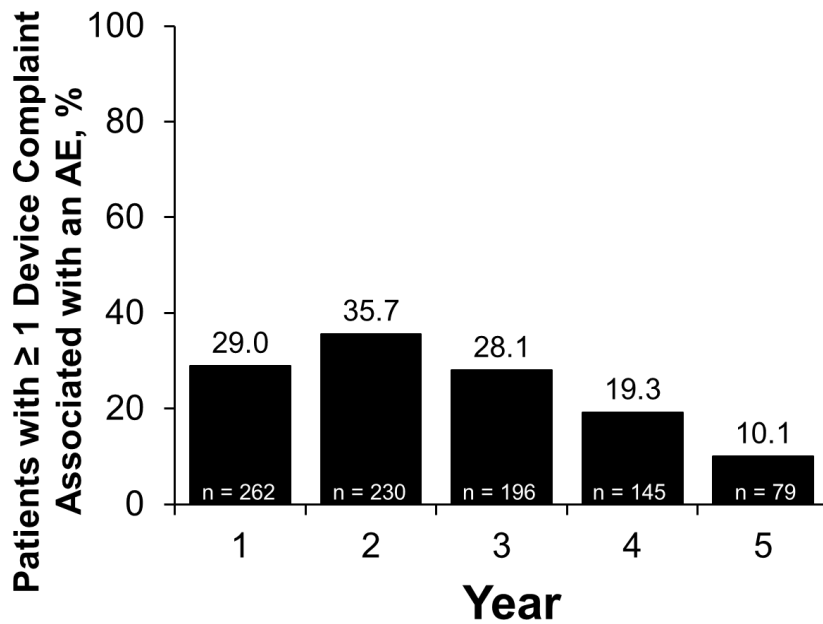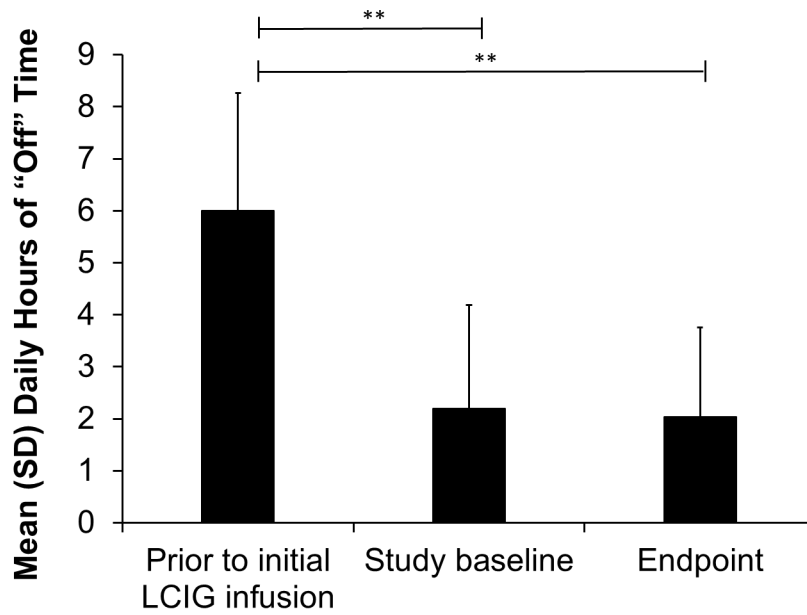
FIG. 1

Status of 262 patients as of September 30, 2015
Converted to commercially available LCIG: n = 110
Ongoing: n = 63
Prematurely discontinued: n = 89
   Primary reasons for discontinuation:
     Adverse event: n = 64 (24%)
     Withdrew consent: n = 15 (6%)
     Lack of efficacy: n = 7 (3%)
     Protocol violation: n = 2 (<1%)
     Administrative: n = 1 (<1%)
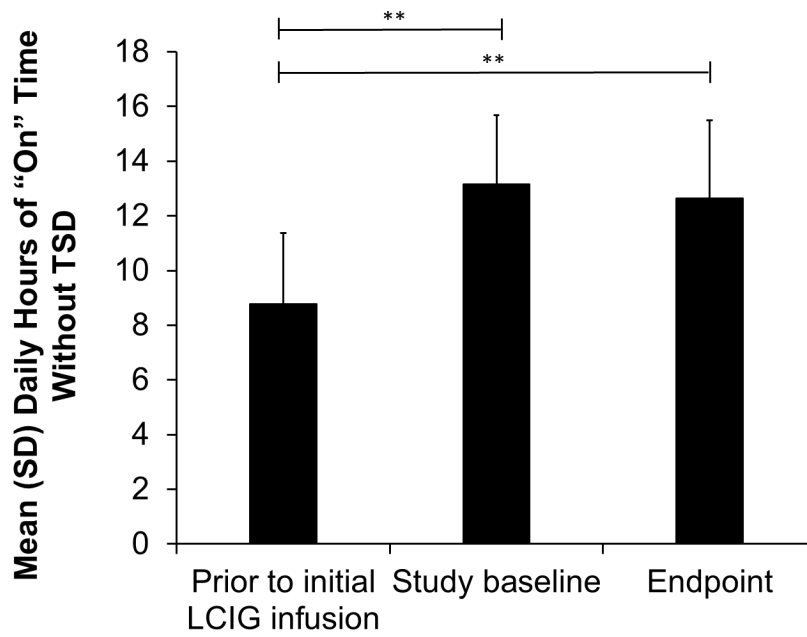
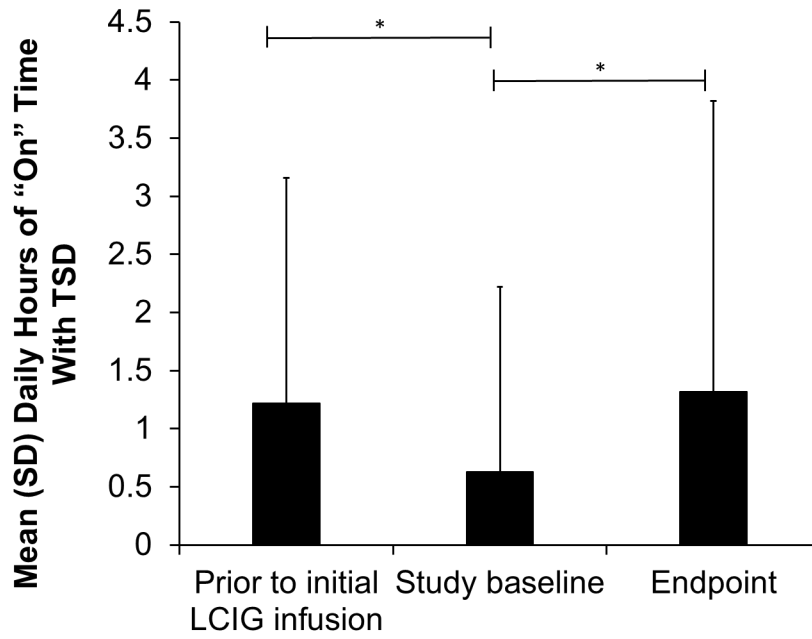FIG. 2

a

b

FIG. 3

a

b

c

SUPPLEMENTAL MATERIAL

SUPPLEMENTAL TABLE 1. Concomitant anti-PD medications by year of treatment

Treatment	Patients, n (%)					
n (%)	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)

PD, Parkinson's disease; LCIG, levodopa-carbidopa intestinal gel.

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

SUPPLEMENTAL TABLE 2. Laboratory values monitoring vitamin status

Parameter	Central laboratory normal range	n	Mean (SD) Study baseline[a]	Mean (SD) Endpoint	Mean (SD) Change from baseline	Patients with values outside normal range, n (%) <LLN[b]	Patients with values outside normal range, n (%) >ULN[b]
Overall population							
Vitamin B6, nmol/L	20.0 – 125.0	119	70.2 (98.5)	94.6 (119.3)	+24.4 (128.7)	151 (72)	98 (46)
Vitamin B12, pmol/L	148.0 – 775.0	126	389.2 (435.4)	562.8 (975.8)	+173.5 (900.7)	19 (9)	44 (21)
Folic acid, nmol/L	4.5 – N/A	87	50.2 (132.1)	40.0 (43.6)	-10.2 (137.0)	2 (0.9)	N/A
Homocysteine, µmol/L	3.7 – 13.9	126	19.5 (9.4)	23.6 (12.8)	+4.1 (11.1)	1 (0.5)	197 (92)
Methylmalonic acid, µmol/L	0.0 – 0.4	127	0.267 (0.222)	0.285 (0.317)	+0.018 (0.223)	N/A	58 (27)
Patients experiencing polyneuropathy-related adverse events[c]							
Vitamin B6, nmol/L	20.0 – 125.0	13	81.48 (118.84)	120.35 (133.12)	+38.87 (119.93)	15 (75)	11 (55)
Vitamin B12, pmol/L	148.0 – 775.0	14	345.2 (298.5)	613.9 (638.6)	+268.7 (398.9)	5 (25)	5 (25)
Folic acid, nmol/L	4.5 – N/A	8	53.86 (83.44)	55.48 (42.55)	+1.61 (79.27)	0	N/A
Homocysteine, µmol/L	3.7 – 13.9	13	19.14 (10.52)	24.68 (13.25)	+5.55 (5.99)	0	18 (90)
Methylmalonic acid, µmol/L	0.0 – 0.4	14	0.401 (0.497)	0.371 (0.629)	-0.030 (0.233)	N/A	5 (25)

[a]Study Baseline is entry into this extension study (ie, after 52 to 74 weeks of LCIG treatment in a previous study).

[b]Patients could fall into both categories at any given time during the study; columns do not add up to 100%.

[c]Includes patients who experienced decreased vibratory sense, demyelinating polyneuropathy, neuralgia, peripheral neuropathy, peripheral sensory neuropathy, polyneuropathy, and sensory disturbance.

SUPPLEMENTAL TABLE 3. Efficacy measurements in United States patients

	Change from:					
	Prior to initial LCIG infusion to study baseline[a]		Prior to initial LCIG infusion to endpoint[a]		Study baseline to endpoint[a]	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
UPDRS total score	79	-7.76 (13.32)[b]	79	9.20 (20.86)[b]	82	16.90 (14.97)[b]
Part II	79	-3.03 (5.66)[b]	79	3.05 (7.76)[c]	82	6.12 (5.47)[b]
Part III	79	-4.77 (10.35)[b]	79	4.60 (14.68)[c]	82	9.27 (10.60)[b]
PDQ-39 summary index	81	-8.10 (12.93)[b]	81	0.50 (16.63)	81	8.60 (13.27)[b]
Mobility	81	-14.20 (19.49)[b]	81	1.14 (27.22)	81	15.34 (22.63)[b]
Daily living	81	-10.55 (20.10)[b]	81	0.82 (28.24)	81	11.37 (20.81)[b]
Emotional well-being	80	-3.13 (18.99)	80	0.16 (19.87)	81	3.24 (17.67)
Stigma	81	-7.72 (21.02)[c]	81	-7.10 (21.44)[c]	81	0.62 (20.72)
Social support	80	1.98 (17.62)	80	3.02 (19.90)	81	1.34 (17.28)
Cognition	81	-4.63 (17.78)[d]	81	4.17 (19.84)	81	8.80 (20.42)[b]
Communication	81	-4.22 (14.08)[c]	81	6.38 (23.06)[d]	81	10.60 (18.87)[b]
Bodily discomfort	81	-11.73 (20.53)[b]	81	-5.35 (23.17)[d]	81	6.38 (17.29)[c]

LCIG, levodopa-carbidopa intestinal gel; PDQ-39, 39-Item Parkinson's Disease Questionnaire; SD, standard deviation; UPDRS, Unified Parkinson's Disease Rating Scale.

[a]"Prior to Initial LCIG Infusion" occurred in a previous study; "Study Baseline" refers to the last assessment in a previous study, which served as a baseline for this open-label extension study; "Endpoint" refers to measurements at the cutoff date for this open-label, extension study.

[b]$P < 0.001$.

[c]$P < 0.01$.

[d]$P < 0.05$.

SUPPLEMENTAL FIG. 1. Percent of patients with ≥ 1 device complaint each year.
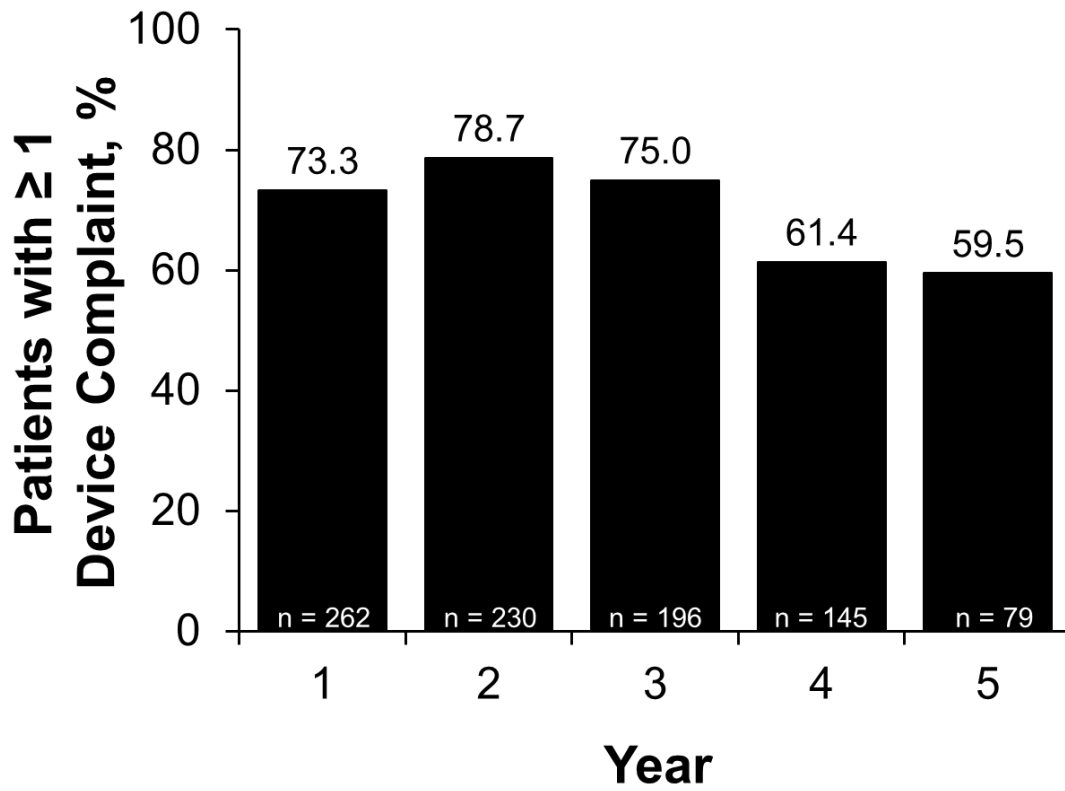
SUPPLEMENTAL FIG. 2. Patients receiving either PEG or J tube replacements based on (a) the total number of tube replacements during the study and (b) the number of tube replacements each year of the study. J, jejunal; PEG, percutaneous endoscopic gastrostomy.

a

b