2.0   Synopsis

AbbVie Inc.	Individual Study Table Referring to Part of Dossier:	(For National Authority Use Only)
Name of Study Drug: Levodopa Carbidopa Intestinal Gel (LCIG)	**Volume:** **Page:**	
Name of Active Ingredient: Levodopa-Carbidopa		

Title of Study:
An Open-Label, Two Part, Multicenter Study to Assess the Safety and Efficacy of Levodopa-Carbidopa Intestinal Gel (LCIG) for the Treatment of Non-Motor Symptoms in Subjects with Advanced Parkinson's Disease

Coordinating Investigator:
David Standaert, MD, PhD

Study Sites:
12 sites in the US, 11 of which enrolled subjects

Publications:
None

Studied Period (Years):
     First Subject First Visit: 06 March 2013
     Last Subject Last Visit: 28 December 2015
	Phase of Development: 3b

Objectives:
The primary objective of this study was to evaluate the change in non-motor symptoms from baseline to Week 12 as measured by the Non-Motor Symptom Scale (NMSS) total score.
The secondary objectives of this study were to assess safety, change from baseline in motor symptoms, health outcomes, and change from baseline in neurocognition.

Methodology:
This was a Phase 3b, single-arm, open-label, two-part, multicenter study to assess the safety and efficacy of LCIG for the treatment of non-motor symptoms in subjects with advanced Parkinson's disease. The study consisted of 2 sequential parts:
- Part 1: A Screening Period (Screening Visits 1, 2 and 3) was followed by percutaneous endoscopic gastrostomy – with jejunal extension (PEG-J) placement (Study Day 1), LCIG initiation, and LCIG treatment for 12 weeks   - Part 2: Long-Term Maintenance (48 weeks in length)

Number of Subjects (Planned and Analyzed):
Planned: 36; enrolled (signed informed consent form): 53; treated with LCIG: 38.
39 subjects analyzed for safety (Safety dataset); 38 subjects analyzed for efficacy (Efficacy dataset).

Diagnosis and Main Criteria for Inclusion:

Subjects with levodopa-responsive advanced Parkinson's disease (PD) who experienced severe motor complications despite optimized treatment with available PD medication and who met the following inclusion criteria were eligible:

- Subject had a diagnosis of idiopathic Parkinson's disease according to the United Kingdom Parkinson's Disease Society (UKPDS) Brain Bank Criteria.
- The subject's Parkinson's disease was levodopa-responsive.
- Subject had had optimal treatment with available anti-PD medication and their symptoms were judged inadequately controlled on this optimized treatment.
- Subject had a recognizable/identifiable "Off" and "On" state (motor fluctuations).
- Subject was experiencing a minimum of 3 hours of "Off" time confirmed by the Parkinson's Disease Diary for each of 3 consecutive completion days prior to Screening Visit 2.
- Subject was a male or female at least 30 years of age.

Subjects were excluded if they met any of the following criteria:

- Subject's PD diagnosis was unclear or there was a suspicion that the subject had a Parkinsonian syndrome such as secondary Parkinsonism (e.g., caused by drugs, toxins, infectious agents, vascular disease, trauma, brain neoplasm), Parkinson-plus syndrome (e.g., multiple system atrophy, progressive supranuclear palsy, diffuse Lewy body disease, corticobasilar cegeneration) or other neurodegenerative disease that might mimic the symptoms of PD.
- Current primary psychiatric diagnosis of uncontrolled acute psychotic disorder or other uncontrolled primary psychiatric diagnoses
- Subject experiencing sleep attacks or clinically significant impulsive behavior.
- Subject had significant current suicidal ideation within 1 year prior to Screening.
- Subject had undergone neurosurgery for the treatment of Parkinson's disease.
- Subject had contraindications to levodopa.
- Subject had any neurological deficit that might interfere with the study assessments (e.g., hemiparesis).
- Subject for whom the placement of a PEG-J tube for LCIG treatment was contraindicated or was considered a high risk for the PEG-J procedure according to the gastroenterology evaluation.
- Known hypersensitivity to levodopa, carbidopa or radiopaque material.

Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:

LCIG was supplied as a homogenous suspension of levodopa (20 mg/mL) and carbidopa monohydrate (5 mg/mL) in an aqueous intestinal gel (carboxymethyl cellulose). The intestinal gel was dispensed in a medication cassette reservoir of 100 mL, designed to be connected to a portable subject-operated pump. LCIG infusion was administered over a full 16-hour period each day.

The total daily dose of infusion LCIG was composed of three components: (i) the morning dose, (ii) continuous maintenance infusion dose and (iii) extra doses.

Subject dosing was determined individually. The starting total daily dose of LCIG infusion after placement of the PEG-J tube was based solely on the daily dose of the oral levodopa component from the tablets of levodopa-carbidopa 100/25 immediate release (LC-IR) taken immediately prior to or at the time of Study Day 1 during the 16-hour waking day it was anticipated the subject would be on LCIG therapy. The rate of LCIG infusion was expected to be within the range of 1 to 10 mL/hour (20 to 200 mg of levodopa/hour) in most instances and run over a period of 16 consecutive hours.

After the 16-hour time frame, levodopa-carbidopa immediate release (LC-IR) or levodopa-carbidopa continuous release (LC-CR) (oral LC) could be taken for nighttime use and was not counted as rescue medication.

The bulk lot numbers are listed below.

Study Drug	Route of Administration	Manufacturer	Bulk Lot Numbers
Levodopa-carbidopa 100 mg/25 mg immediate release (LC-IR) tablets	Oral	▮▮▮▮▮	11-005478 13-000520 13-006254
100 mL Levodopa (20 mg/mL)-carbidopa (5 mg/mL) intestinal gel (LCIG) medication cassette reservoirs	Upper-intestinal infusion	▮▮▮▮▮	12-006132 12-007700 14-001745 14-004130 14-006609 15-000707 15-001947

Duration of Treatment:

The duration of LCIG treatment was to be 60 weeks.

Subjects who completed their Week 60 visit before LCIG was commercially available had the option to extend their LCIG therapy, if in the opinion of the investigator, the subject would benefit from continued LCIG treatment.

Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:

Not applicable.

Criteria for Evaluation

Efficacy:

The primary efficacy variable was the change from baseline to Week 12 in the NMSS total score.

Additional efficacy variables included the following:

- Change from baseline in the NMSS domain scores
- Change from baseline in the NMSS total score at other scheduled time points.
- Average daily "Off" time as collected by the Parkinson's Disease Diary
- Average daily "On" time without troublesome dyskinesia as collected by the Parkinson's Disease Diary
- Unified Parkinson's Disease Rating Scale (UPDRS) total score and section scores during "On" time
- Cambridge Neuropsychological Test Automated Battery (CANTAB) Spatial Working Memory (SWM)
- Controlled Oral Word Association Test (COWAT) Verbal Fluency

Health Outcomes:

Health outcomes were assessed with the Parkinson's Disease Questionnaire-39 (PDQ-39), Patient Global Impression of Change (PGIC), Treatment Satisfaction Question (TSQ), and Health-Related Productivity Questionnaire (HRPQ).

Safety:

Safety and tolerability over the course of the study was assessed by the following measurements:

- Adverse event monitoring
- Number of hospital admissions and total days hospitalized
- Health Resource Utilization Questionnaire (HRUQ)
- Clinical laboratory evaluations
- Electrocardiogram
- Vital signs and weight
- Columbia Suicide-Severity Rating Scale (C-SSRS)
- Sleep Attack Assessment
- Minnesota Impulsive Disorders Interview (MIDI)
- Product Quality Complaints

Statistical Methods

Efficacy:

The Efficacy dataset included all subjects who received at least 1 infusion of LCIG study drug and had a baseline and LCIG Treatment Period observation for at least one efficacy or health outcome measure.

Statistical Methods (Continued)

Efficacy (Continued):

The primary efficacy analysis was the change from baseline to Week 12 in the NMSS total score. The change from baseline was estimated using a mixed-effect repeated measures model (MMRM) that included the fixed effects of study site and visit, with baseline score as a covariate, and the baseline-by-visit interaction. As pre-specified in the statistical analysis plan (SAP), the first-order autoregressive (AR1) covariance structure was used to estimate the within subject variance-covariance structure because the model did not converge when the unstructured covariance structure was used and Satterthwaite's approximation was used to estimate the denominator degrees of freedom. Type III sums-of-squares and least-square (LS) means were used for statistical comparisons. The analysis did not include data collected after the last dose of LCIG. The LS mean and 95% confidence interval obtained from the model were presented.

Additional analyses of efficacy included the change from baseline in motor symptoms as measured by the Parkinson's Disease Diary and UPDRS, and the change in neurocognition as measured by the cognitive battery.

The NMSS domain scores, mean daily "Off" time as measured by the PD Diary, and mean daily "On" time without troublesome dyskinesia as measured by the PD Diary were analyzed with the same MMRM model as the primary efficacy variable. The UPDRS total and section scores were analyzed with the same MMRM model except an unstructured covariance structure was used.

These efficacy variables were also summarized by descriptive statistics (number of subjects with non-missing data, mean, standard deviation, median, minimum and maximum) at baseline, at each scheduled visit and at the final visit. The change from baseline was presented and the hypothesis of no change was evaluated with a one-sample t-test.

A Completers dataset was used to perform post-hoc sensitivity analyses of the NMSS total score, NMSS domain, and PD Diary endpoints. The Completers dataset included the subset of subjects in the Efficacy dataset who completed the planned 60 weeks of LCIG study drug.

Health Outcomes:

The Efficacy dataset was used to summarize heath outcome measures.

The PDQ-39 summary index score and domain scores were analyzed with the same MMRM model as the primary efficacy variable, except an unstructured covariance structure was used. They were also summarized by descriptive statistics (number of subjects with non-missing data, mean, standard deviation, median, minimum and maximum) at baseline, at each scheduled visit and at the final visit. The change from baseline was presented and the hypothesis of no change was evaluated with a one-sample t-test.

The PGIC, TSQ, and HRPQ data were summarized by descriptive statistics. Continuous variables were summarized by the number of subjects with non-missing data, mean, standard deviation, median, minimum and maximum. Categorical variables were summarized by the number of subjects with non-missing data and the number and percentage of subjects in each response category.

Safety:

The Safety dataset included all subjects who underwent the PEG-J placement procedure. The Safety dataset was used to summarize safety data during the LCIG Treatment Period.

Safety was assessed by monitoring for adverse events and product quality complaints, hospitalizations and health resource use as measured by the HRUQ, clinical laboratory evaluations, vital signs, and electrocardiograms (ECGs).

Statistical Methods (Continued)

Safety (Continued):

Treatment-emergent adverse events (TEAEs) were summarized by system organ class and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA).

Laboratory variables, including changes from baseline, were summarized. Shift tables were presented according to the reference ranges (low, normal, or high). A frequency table was presented for potentially clinically significant (PCS) abnormal values.

Vitals signs and ECG parameters, including changes from baseline, were summarized. A frequency table was presented for PCS abnormal values.

For Product Quality Complaints (PQCs), a frequency table was presented. A frequency table was presented for sleep attacks, excessive impulsive behavior, and suicidal ideation or behavior on the C-SSRS.

Summary/Conclusions

Efficacy Results:

A total of 39 subjects with a mean age of 64.3 years (range: 43.0 years to 84.0 years) and a mean body mass index (BMI) of 26.2 kg/m^2 were enrolled and 38 of these subjects were treated with LCIG. 28 of the subjects completed 60 weeks of LCIG treatment.

Primary Efficacy Variable: The primary endpoint, change in LS mean change in NMSS total score from baseline to Week 12 by the MMRM model, was –17.6 (95% CI: –24.7, –10.4), indicating improvement in non-motor symptoms in subjects who received LCIG, and this improvement was statistically significant ($P < 0.001$). Thus, the primary null hypothesis was rejected in favor of the primary alternative hypothesis, and LCIG treatment resulted in statistically significant improvement on NMSS total score.

Secondary Efficacy Variables:

NMSS Scores

Statistically significant improvement (decrease) from baseline in LS mean NMSS total score occurred early (by Screening Visit 3). The magnitude of improvement (decrease) from baseline in LS mean NMSS total score at Week 4 (–13.8) was greater than at Screening Visit 3 (–7.9). Statistically significant improvement from baseline in LS mean NMSS total score was maintained though Week 60.

The LS mean directional change from baseline in NMSS domain scores was generally similar to LS mean change from baseline in NMSS total scores. The mean NMSS domain scores that improved (decreased) statistically significantly from baseline to the Week 12 Visit were sleep/fatigue, attention/memory, gastro-intestinal tract, urinary, sexual function, and miscellaneous. Improvement in mean NMSS domain scores from baseline to the Week 60 Visit was statistically significant for the same domain scores, except for the urinary domain score.

Mean Daily "Off" Time and Mean Daily "On" Time Without Troublesome Dyskinesia

Consistent with observations in earlier clinical studies of LCIG, motor symptoms also improved from baseline with LCIG treatment in this study, based on PD diary data. LS mean daily normalized "Off" time was statistically significantly improved (decreased) from baseline by Day 7 of the LCIG Treatment Period (–1.4 hours, $P < 0.001$). LS mean daily normalized "Off" time decreased further by Week 4 (–3.5 hours), and this improvement was maintained through the 60-week LCIG Treatment Period (e.g., –4.1 hours at Week 12 and –4.9 hours at Week 60).

Summary/Conclusions (Continued)

Efficacy Results (Continued):

In this study, the observed improvements (decreases) in mean daily normalized "Off" time were complemented by improvements (increases) in mean daily "On" time without troublesome dyskinesia (a composite of "On" time without dyskinesia + "On" time with non-troublesome dyskinesia) and mean "On" time without dyskinesia, as measured by PD diary data. Improvement (increase) from baseline in the LS mean for "On" time without troublesome dyskinesia and "On" time without dyskinesia was statistically significant by Day 7 of LCIG treatment, further improvement occurred by Week 4, and this improvement was maintained through the 60-week LCIG Treatment Period. In contrast, LS mean "On" time with non-troublesome dyskinesia or "On" time with troublesome dyskinesia did not increase or decrease consistently from baseline, and the changes observed in these parameters were not statistically significant at most time points. Furthermore, the LS mean increase from baseline in "On" time without troublesome dyskinesia (3.6 hours at Week 4 and 4.3 hours at Week 60) was accounted for by increase in "On" time without dyskinesia (4.0 hours at Week 4 and 4.3 hours at Week 60) and not "On" time with non-troublesome dyskinesia (decreases of 0.6 hours at Week 4 and 0.1 hours at Week 60).

UPDRS Score

Mean UPDRS total and section scores were improved (decreased) from baseline during LCIG treatment. Improvement from baseline to Day 7 of the LCIG Treatment Period in LS mean was statistically significant for UPDRS total score ($P < 0.001$) and all UPDRS section scores ($P \leq 0.008$), and the LS mean for Part IV indicated more improvement from baseline on Day 7 (2.7) than at Screening Visit 3 (0.7). Improvements (decreases) from baseline in LS mean UPDRS total, UPDRS Part II (activities of daily living [ADLs]) section, Part IV (Complications of therapy) section, and Dyskinesia items scores were maintained through the LCIG Treatment Period, as improvements from baseline in LS means were statistically significant ($P \leq 0.002$) for UPDRS total scores at Week 4, Week 12, Week 36, and Week 60.

Neurocognition

No statistically significant change from baseline to Week 12 or the Final Visit was observed in mean CANTAB SWM Between Errors or Strategy scores or mean COWAT All Letters and Baseline Letters scores. These findings were consistent with the lack of statistically significant LS mean changes in NMSS cognition domain scores over time in this study.

Health Outcomes Results:

Subjects in the Efficacy dataset generally reported that HRQoL improved with LCIG treatment and they were satisfied with LCIG treatment, on the basis of PDQ-39, PGIC, and TSQ results.

The PGIC scores indicated a majority of subjects considered their status to be improved (minimally improved, much improved, or very much improved) at Week 12 (78.9%) and Week 60 (71.1%), and no subjects considered their status to be much worse or very much worse at these time points. The percentage of subjects who reported being very satisfied with treatment on the TSQ increased markedly from baseline during LCIG treatment, demonstrating that the percentage of subjects who were very satisfied with their Parkinson's disease treatment was markedly increased from baseline.

On the HRPQ, there was a mean decrease from baseline in the total number of hours of lost work in the workplace and in the household at all timepoints. LCIG significantly improved work productivity at Week 60 as demonstrated by the reduction from baseline in the total hours of work lost in the workplace, the total percentage of planned work lost in the workplace, and the total percentage of planned work lost in the household.

Summary/Conclusions (Continued)

Safety Results:

Overview of Adverse Events

Overall, 94.9% of subjects in the Safety dataset experienced at least 1 TEAE during the study. Treatment-emergent adverse events were considered by the investigator to have a reasonable possibility of being related to LCIG in 89.7% of subjects and of being related to oral LC in 28.2% of subjects. Severe TEAEs were reported in 12.8% of subjects, serious TEAEs occurred in 20.5% of subjects, and TEAEs led to premature discontinuation in 12.8% of subjects. Gastro-intestinal TEAEs were reported in 71.8% of subjects overall.

For the above categories of TEAEs, the percentage of subjects was numerically lower during Weeks 1 – 4 of LCIG treatment (immediately after PEG-J placement) than during the later time period, Weeks 5 – 60 of LCIG treatment, with one exception. This was consistent with the longer duration of the latter time period. The exception was gastrointestinal (GI) TEAEs, which occurred in similar percentages of subjects during Weeks 1 – 4 and Weeks 5 – 60, but this finding is consistent with subjects having undergone GI surgery for PEG-J placement just prior to Weeks 1 – 4.

There was 1 death during the study due to severe, serious TEAEs that were considered by the investigator and AbbVie to have no reasonable possibility of being related to LCIG. There were no pregnancies reported during the study.

No action was taken with study drugs as a result of serious TEAEs, with the exception of a 21-day interruption of study drugs at Day 262 in 1 subject due to 2 serious TEAEs (major depression and suicidal ideation), a delay in LCIG initiation until Day 7 in another subject due to a serious TEAE (peritonitis), and premature discontinuation of study drugs in a subject who experienced 3 serious, fatal TEAEs that were considered to have no reasonable possibility of being related to study drugs (acute respiratory failure, aspiration pneumonia, and congestive heart failure).

Treatment-Emergent Adverse Events

Overall, the most common TEAEs (occurring in > 10% of subjects in the Safety dataset overall) were procedural pain (33.3%), stoma site infection (28.2%), stoma site pain (23.1%), anxiety (20.5%), stoma site erythema (20.5%), fall (17.9%), weight decreased (17.9%), urinary tract infection (15.4%), orthostatic hypotension (12.8%), excessive granulation tissue (10.3%), flatulence (10.3%), nausea (10.3%), stoma site irritation (10.3%), and vitamin B_6 deficiency (10.3%). The most common TEAE, procedural pain, occurred in a numerically higher percentage of subjects during Weeks 1 – 4 (immediately after PEG-J placement), compared to during the longer, subsequent LCIG Treatment Period (Weeks 5 – 60), as expected for subjects who had more recently undergone PEG-J placement during Weeks 1 – 4 than during Weeks 5 – 60.

Summary/Conclusions (Continued)

Safety Results (Continued):

Severity of TEAEs

The majority of TEAEs were mild or moderate in severity. The most common TEAE in the Safety dataset with a maximum severity of moderate or severe during Weeks 1 – 4 was moderate procedural pain (7.7%). The only severe TEAE with an onset during Weeks 1 – 4 was peritonitis in 1 subject. The most common TEAE in the Safety dataset with a maximum severity of moderate or severe during Weeks 5 – 60 was weight decreased (15.4%). This pattern was consistent with subjects who had more recently undergone PEG-J placement in Weeks 1 – 4 than in Weeks 5 – 60. Progressive weight loss is common in subjects with PD and could be related to impaired olfaction, motor slowness, and dysphagia. In addition, weight loss is associated with administration of levodopa. In the LCIG clinical program, no clear predictive factors for the development of weight loss have been identified. Weight loss is considered a potential risk with LCIG treatment and is being monitored.

Adverse Events of Special Interest (AESI)

The polyneuropathy standardized MedDRA Query (SMQ) (broad and narrow search), weight loss company MedDRA query (CMQ), respiratory tract aspiration CMQ, and GI and GI procedure CMQ were utilized to identify AESIs. The polyneuropathy SMQ (narrow search) identified TEAEs in 3 (7.7%) subjects in the Safety dataset, and these TEAEs were generally mild or moderate in severity, non-serious, and did not occur during Weeks 1 – 4 of LCIG treatment. The weight loss CMQ identified TEAEs in 8 (20.5%) subjects in the Safety dataset. The most common TEAE identified with the weight loss CMQ was weight decreased in 7 (17.9%) subjects. The TEAEs identified with the weight loss CMQ were generally mild or moderate in severity and non-serious. The respiratory tract aspiration CMQ identified TEAEs in 7 (17.9%) subjects in the Safety dataset. No TEAE identified with the respiratory tract aspiration CMQ occurred during Weeks 1 – 4 and no preferred term was identified in more than 2 (5.1%) subjects. The TEAEs identified with the respiratory tract aspiration CMQ were generally mild or moderate in severity.

The GI and GI procedure CMQ identified TEAEs in 28 (71.8%) subjects in the Safety dataset. The most common TEAEs identified with this CMQ (reported in > 20% of subjects overall) were not unexpected in subjects who recently underwent PEG J placement, and were procedural pain (33.3%), stoma site infection (28.2%), stoma site pain (23.1%), and stoma site erythema (20.5%). Procedural pain was reported in a numerically higher number of subjects during Weeks 1 – 4 (immediately after PEG-J placement) (33.3%) than during Weeks 5 – 60 (5.1%); the reverse trend occurred for stoma site infection, stoma site pain, or stoma site erythema. The TEAEs identified with the GI and GI procedure CMQ were mild or moderate in severity, with the exception of a severe, serious TEAE of peritonitis in 1 subject.

Product Quality Complaints

A total of 87.2% of subjects in the Safety dataset reported PQCs, and 59.0% of subjects reported a PQC that was linked to an AE. The most common preferred terms in subjects with PQCs linked to an AE (reported in > 10% of subjects overall) were: stoma site infection (25.6%), stoma site erythema (15.4%), excessive granulation tissue (10.3%), and stoma site discharge (10.3%).

Clinical Laboratory Test Results

Overall, the observed mean changes from baseline to scheduled visits in hematology, clinical chemistry, urinalysis, special laboratory test values, and ECG values were not considered to be clinically meaningful.

Summary/Conclusions (Continued)

Safety Results (Continued):

Vital Signs

The most common PCS vital signs were body weight decreased ≥ 7% from baseline (60.5% of subjects) orthostatic (change from supine to standing) SBP ≥ 30 mmHg decrease from baseline (26.3%), and orthostatic DBP ≥ 20 mmHg decrease from baseline (23.7%). Among the 23 subjects who experienced PCS body weight decreased ≥ 7% from baseline, 7 subjects experienced at least one relevant, temporally associated TEAE, including weight decreased, dysgeusia, nausea, vomiting, dysphagia, and/or dehydration.

Conclusions:

The present study provides evidence for improvements in non-motor and motor symptoms and health outcomes with LCIG treatment, and for the safety of LCIG treatment in levodopa-responsive subjects with advanced PD. The primary efficacy endpoint was mean change in NMSS total score from baseline to Week 12 and the LS mean of the change by the MMRM model was –17.6 (95% CI: –24.7, –10.4), indicating statistically significant improvement ($P < 0.001$). Statistically significant improvement from baseline in mean NMSS total score occurred by Screening Visit 3 and was maintained at Week 60 of LCIG treatment. Mean improvement in non-motor symptoms from baseline was statistically significant for the following NMSS domains at both Week 12 and Week 60 of LCIG treatment: sleep/fatigue, attention/memory, gastro-intestinal tract, sexual function, and miscellaneous.

Consistent with observations in previous clinical studies of LCIG, motor symptoms (mean daily "Off" or "On" time and UPDRS total and section scores) were also improved from baseline during LCIG treatment. Mean daily "On" time without troublesome dyskinesia (a composite of "On" time without dyskinesia + "On" time with non-troublesome dyskinesia) and mean "On" time without dyskinesia improved (increased) from baseline over time, complementing the observed improvements (decreases) in "Off" time. These mean improvements from baseline were statistically significant by Day 7, statistically significant at every time point measured, and clinically meaningful. In addition, the use of anti-PD medications was markedly reduced, and the quality of sleep may have improved with LCIG treatment.

Subjects in the Efficacy dataset reported improved HRQoL with LCIG treatment and satisfaction with LCIG treatment, on the basis of PDQ-39, PGIC, and TSQ results.

The HRPQ results showed that LCIG significantly improved work productivity at Week 60 as demonstrated by the reduction from baseline in the total hours of work lost in the workplace, the total percentage of planned work lost in the workplace, and the total percentage of planned work lost in the household.

The safety profile in this study was consistent with the profile in previous clinical studies of LCIG, confirming overall tolerability and safety of this system.