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Oral Levodopa Formulation Does Not Affect Progression of Parkinson's Disease

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Abstract

Objective.—Motor fluctuations develop in most patients treated with carbidopa/levodopa for Parkinson's disease (PD). The continuous dopamine stimulation (CDS) hypothesis suggests that longer-acting forms of levodopa might improve outcomes, but this has been inadequately tested in humans. We undertook to determine if there is any difference in symptom progression rate among patients taking immediate-release carbidopa/levodopa (IR), controlled-release carbidopa/levodopa (CR), or carbidopa/levodopa/entacapone (CLE) using standard outcome measures in a naturalistic study.

Methods.—We evaluated PD subjects prospectively followed for up to 48 months in the Parkinson's Disease Biomarker Project. Bayesian linear or generalized linear mixed effects models were developed to determine if oral levodopa formulation influenced the rate of symptom progression as measured by 8 outcome measures.

Results.—At baseline, the IR, CR and CLE groups were similar except that the CR group had milder disease and was represented at only one site, and the CLE group had a longer disease duration. In the primary analysis, there was no difference in rate of symptom progression as measured by the MDS-UPDRS part II, part IV or total score. In the secondary exploratory analysis, there was no difference in progression rate as measured by change in levodopa equivalent daily dose, Montreal Cognitive Assessment, Parkinson's disease questionnaire mobility subscore, Schwab and England Activities of Daily Living Scale, or a global composite outcome.

Conclusions.—We found no difference in symptom progression rate in patients taking IR, CR or CLE. This clinical observation supports pharmacokinetic studies demonstrating that none of these oral levodopa formulations achieve CDS.

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Keywords

Parkinson disease; levodopa; progression; rate; formulation

INTRODUCTION

Parkinson disease (PD) is the second most common neurodegenerative disease with a direct relationship to aging (1). As the world's population ages, some have refered to the anticipated rise in PD cases as a pandemic (2). While levodopa is widely recognized as the most effective drug for PD (3), it is associated with motor fluctuations and dyskinesias that degrade health-related quality of life (4, 5). Studies in both animals (6) and humans (7) comparing long acting dopamine agonists to levodopa have led to the continuous dopamine stimulation (CDS) concept for treating PD in which physicians select dopaminergic drugs with longer half-lives in an effort to delay or reduce motor fluctuations and dyskinesias. In general, these studies show that treatment with dopamine agonists are associated with fewer motor complications at the expense of less overall benefit and a greater side effect profile.

In light of these tradeoffs, the ideal pharmacological treatment for PD would be an oral formulation of levodopa with a long half-life that could achieve CDS without the side effect baggage of dopamine agonists. Controlled-release carbidopa/levodopa tablets (Sinemet CR, Merck & Co., Inc., 1996) were developed in hopes of achieving this goal. According to the package insert, this agent utilizes a polymeric-based drug delivery system that produces "less variation in plasma levodopa levels than with carbidopa/levodopa immediate release tablets (8)." In 1999, a double-blind, randomized study comparing controlled-release carbidopa/levodopa (CR) and immediate-release carbidopa/levodopa (IR) in levodopa naïve subjects was published. A total of 616 patients with a mean disease duration of 2.3 years were randomized to IR or CR given twice daily and followed for 5 years. During the study, titration of the dose and adjustment of the dosing frequency was permitted. The primary endpoint was time to onset of motor fluctuations. The results were that by the end of the study, the IR group required 3.6 doses per day while the CR group took 3.2 doses per day which was a statistically significant difference. However, there was no difference in the probability of developing motor fluctuations by 5 years which was 16% in both groups (9).

Because this study showed that there was no benefit from CR at reducing the risk of motor fluctuations, some interpreted this as evidence against the CDS hypothesis. The American Academy of Neurology published a now retired guideline stating that "sustained release carbidopa/levodopa … may be disregarded to reduce off time (Level C) (10)." However, because the half-lives of both IR and CR do not exceed two hours (11), we reasoned that twice daily dosing with these agents could not possibly provide continuous dopamine receptor stimulation, and that therefore this negative study was not evidence against this hypothesis. Moreover, most physicians recognize that twice daily administration of any form of levodopa produces inadequate efficacy, so the general practice is to administer this agent at least three times daily. We undertook to utilize the resource of the Parkison's Disease Biomarker Program (12, 13) to determine if various oral levodopa preparations administered at least three times daily for up to 4 years were associated with differences in any of several

outcome variables. Our hypothesis was that no difference would be found with regard to motor fluctuations and other complications among the three treatment groups because given their serum half-lives, none were suspected of achieving CDS.

MATERIALS AND METHODS

Standard protocol approvals, registrations, and patient consents

The study protocol was reviewed and approved by the Institutional Review Board of the University of Texas Southwestern Medical Center, and at the other institutions where subjects were recruited and followed as part of this project. Written informed consent was obtained from all participants. The study was registered on clinicaltrials.gov with registration number NCT01767818.

Subjects

Subjects with PD were recruited and followed for up to 4 years at UT Southwestern Medical Center, John's Hopkins University School of Medicine, and PennState Health Milton S. Hershey Medical Center between 2012 and 2017 as part of the Parkinson's Disease Biomarker Program (PDBP) established by the National Institutes of Neurologic Disorders and Stroke, USA. Participants had a diagnosis of idiopathic PD according to UK Brain Bank Criteria (14), were male or female age 30 years old or older at the time of diagnosis, if untreated with dopaminergic agents had confirmation of dopamine transporter deficit by I-123 Ioflupane SPECT (DatScan), and if treated with dopaminergic agents had clinical evidence of a favorable response to treatment. Subjects were excluded from this analysis if they had confirmed or suspected atypical parkinsonian syndromes due to drugs, metabolic disorders, encephalitis, or degenerative diseases. Most subjects were initiated on dopaminergic treatment before beginning participation in this project according to the judgment of their treating physician, though a few were de-novo, untreated with dopaminergic drugs, at study entry.

Outcome measures

Throughout the longitudinal study, clinical scales were performed at 6 or 12 month intervals. From the scales available in the PDBP dataset, we designated the following as outcomes for measuring symptom progression which were collected every 6 months: Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part II, IV, and total score (15), and levodopa equivalent daily dose (LEDD) calculated according to Tomlinson and others (16). Outcomes for measuring symptom progression that were obtained every 12 months were: Montreal Cognitive Assessment (MoCA) (17), Parkinson's disease questionnaire (PDQ-39) (18), and Modified Schwab and England Activities of Daily Living Scale (S&E) (19). We also calculated a global composite outcome (GCO) which combines parts I–III of the MDS-UPDRS, S&E, and MoCA according to the method of Fereshtehnejad and others (20). Because a change of raters at one PDBP longitudinal site introduced an anomaly in the MDS-UPDRS part III data at visits following the 12-month assessment, we censored MDS-UPDRS total scores from that site at visits from 18 months onward.

Participant grouping

In order to evaluate differences in symptom progression over time according to levodopa formulation, subjects were stratified based on the levodopa formulation they were taking at study entry: 1) immediate-release carbidopa/levodopa tablets (IR), 2) controlled-release carbidopa/levodopa tablets (CR), or 3) immediate-release carbidopa/levodopa with entacapone (CLE). Subjects were designated as taking CLE if they took IR tablets + entacapone tablets and/or carbidopa/levodopa/entacapone tablets. All three levodopa formulation groups could be taking other dopaminergic drugs such as monoamine oxidase inhibitors, dopamine agonists and amantadine, but subjects were excluded from this analysis if they were taking more than one formulation of levodopa. Later visit data was censored at the time a participant switched to a different levodopa formulation or a second levodopa formulation was added. Subjects were excluded if they were taking levodopa less than 3 times per day.

Analytic plan

To test for potential differences in symptom progression rates between groups, Bayesian linear or generalized linear mixed effects models were fit independently to each of the following 8 progression measurements: 1) MDS-UPDRS Part II score, 2) MDS-UPDRS Part IV score, 3) MDS-UPDRS total score, 4) MoCA, 5) S&E, 6) PDQ-39 mobility subscale, 7) GCO, and 8) LEDD. Specifically, MDS-UPDRS Part II, Part IV, MoCA, and PDQ-39 mobility subscores were modeled using a negative binomial response distribution, MDS-UPDRS total score was modeled using lognormal response distribution, S&E was modeled using a cumulative logit response distribution, GCO was modelled using a Student's *t* response distribution, and LEDD was modelled using a Gaussian response distribution. Furthermore, MoCA scores were reversed such that larger scores indicate greater progression by subtracting all MoCA scores from 30, S&E scores were reversed and converted to integers by multiplying Schwab and England scores by 10 and subtracting the resulting value from 11 such that larger scores indicate greater progression, PDQ-39 scores were converted to integers by multiplying the respective PDQ-39 score by 0.4, and LEDD was converted from mg to dg by dividing the LEDD by 100.

Covariates included in the linear mixed effects or generalized mixed effects models were group-specific intercepts (i.e., intercepts specific to each levodopa administration group), site-specific intercepts, initial non-levodopa PD medication LEDD, group-specific rate of change (that is monthly progression rates specific to each levodopa formulation group), site-specific monthly progression rates, and change in non-levodopa PD medication LEDD relative to baseline LEDD. Additionally, for those progression measurements not including LEDD, IR levodopa equivalent daily dosage (IR-LEDD) at baseline and change in IR-LEDD from baseline were included in the mixed effects regression models. Lastly, subject-specific random intercepts and slopes were included in all models.

The primary analyses for this study include the three-way comparison between the three groups at baseline, as well as their progression rates for the MDS-UPDRS total score, MDS-UPDRS Part II score, and MDS-UPDRS Part IV score. For the primary analyses, the estimated two-sided Bayesian p-values were adjusted using the Šidák correction (21). The

primary analysis assessed for change over time in subjective patient-reported symptoms, objective motor scores, and the presence and severity of motor fluctuations and dyskinesias.

Secondary analyses included the three-way comparison between the groups at baseline and changes over time in MoCA, Schwab and England, PDQ-39 mobility subscale, GCO, and LEDD. Because this analysis was exploratory, we did not adjust p-values for multiple comparisons in the secondary analysis. These results should therefore be interpreted with caution due to the inflation in Type I error intrinsic to multiple testing. All observations with missing covariates were removed. For instance, if the j-th observation for the i-th subject was missing any covariates, that observation was removed but the remainder of observations for the i-th subject with complete covariates remained in the model.

All analyses were performed in R (version 3.6.1) (22). Bayesian linear or generalized linear mixed effects models were run using the brms package in R (23). Weakly informative priors were implemented due to limited prior knowledge. All models were initially run using 3 chains with 15,000 iterations with 5,000 iterations included in the warm-up in order to determine convergence to a stationary distribution. After determining convergence, the model was re-run using single change chains with 15,000 iterations with 5,000 iterations included in the warm-up. Model fitting was examined based on the posterior predictive distribution. Graphs were generated using Prism version 8 (GraphPad Software, LLC).

RESULTS

A total of 233 subjects were classified by treatment with oral levodopa formulation as IR (n=152), CR (n=53), or CLE (n=28) at study entry. Table 1 shows the demographic and clinical outcome data at baseline for the three groups. All CR subjects were followed at UT Southwestern, indicating significant site differences in the use of the various levodopa formulations. Other potentially important differences between groups were that the CR group had generally milder disease (as measured by the MDS-UPDRS), the CLE group was generally younger at diagnosis, and the CLE group had a substantially longer disease duration. Otherwise, the groups were similar.

The results of the three-way primary analyses evaluating annual rate of change in MDS-UPDRS part II, part IV and total scores are shown in Table 2. The data show that there is no significant difference in PD symptom progression rate in activities of daily living, motor complications, or overall motor function in subjects taking the different formulations of levodopa. The secondary analyses evaluating MoCA, S&E, PDQ-39 mobility subscale, GCO, and LEDD as outcome measures are shown in Table 3. These results generally show no significant differences in symptom progression rate when comparing IR, CR, and CLE groups. A single possibly significant difference was seen in comparing the CR and IR groups with respect to the GCO outcome, but we have no confidence in this difference because of multiple testing of the secondary analyses.

The change in scores over time by group in MDS-UPDRS part II, PDQ-39 mobility score, and MoCA is shown in Figure 1 which demonstrates visually the lack of differences in symptom progression.

DISCUSSION

Our results show that there is no difference in PD symptom progression as measured by a number of clinically-relevant endpoints between subjects taking IR, CR or CLE over a period of up to 48 months. This finding is important because we compared subjects taking these agents three or more times daily in the manner in which these drugs are commonly used in the treatment of PD. We believe the failure to find a difference in symptom progression is because none of the tested agents produce CDS. It is also true, however, that because CDS has not been achieved with currently available drug therapies, it remains unknown if achieving CDS would prevent the development of motor complications. Another possible explanation for our negative finding was that our study was underpowered to detect a difference that might exist.

The study by Hsu and others is of particular interest (11). They recuited 24 healthy subjects without PD of which 22 completed the study. Subjects were randomized to receive a single dose under fasted condtions of IR 25/100, CR 25/100, or CLE 25/100/200 following which peripheral blood was collected to measure levodopa plasma concentration at intervals from 15 minutes to an hour over a 12 hour period following dosing. They found that the half-life of plasma levodopa from these three agents was identical at 1.6 hours, and that the time to reaching the peak of the plasma levodopa concentration (T_{max}) was 1 hour for IR and 1.5 hours for CR and CLE. This study demonstrated that CR and CLE do not lengthen the duration of effect of levodopa, rather they simply slow its absorption into the blood stream. Likewise, a study of multiple dose administration of IR and CLE in healthy volunteers and PD subjects demonstrated no significant difference in variability of levodopa plasma concentration when both drugs were administered four times daily at 3.5 hour intervals (24). Another study compared pharmacokinetic (PK) profiles of CR with CLE in 17 patients with PD (25). While the CLE group had less off time than the CR group, there was minimal difference in PK between the groups. Taken together, this body evidence provides strong support for the assertion that none of these formulations of levodopa achieve CDS, and that all three have similar plasma pharmacokinetic profiles.

An important 4-year randomized clinical trial explored the difference in rate of dyskinesia and time to onset of motor fluctuations in PD subjects assigned to IR vs CLE in which both groups received the drug administered four times daily (26). The results were that the CLE group had a greater risk of developing dyskinesia, and that the two groups developed the onset of wearing off at about the same time (73–79 weeks). The authors interpreted the increase in dyskinesia risk as being due to the higher levodopa dose equivalents in the CLE group, and the lack of a difference in onset of motor fluctuations as being due to failure to achieve continuous dopaminergic stimulation even with four times daily administration of levodopa. Given a serum half-life of only 1.6 hours with both IR and CLE, we agree with this conclusion.

Limitations of our study include the non-randomized assignment of subjects to different oral formulations of levodopa, the asymmetric number of subjects in the various groups, the lack of even distribution of levodopa formulations at the three sites, the need to censor UPDRS part III data at one site after the 12 month visit due to a data anomaly introduced by a change

of rater, and the variable length of follow-up caused by subjects entering the study at different times. An additional limitation is that many subjects were taking other dopaminergic drugs in addition to levodopa such that our study is not a pure comparison of three different levodopa formulations. Strengths of our study and analysis include the prospective data collection of standardized outcome measures, the relatively large population studied, and the robust statistical methods used to avoid capitalization on chance.

It is our view that with respect to oral levodopa treatment, the continuous dopaminergic stimulation hypothesis has not yet been adequately tested in humans. We are hopeful that future naturalistic studies of longer acting levodopa formulations and delivery methods will be conducted to determine the best way to address the dopamine deficiency in PD.

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Conflicts of Interest and Source of Funding:

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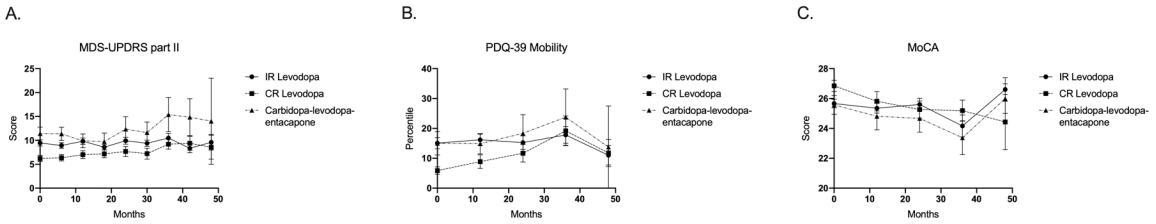

Figure 1.

Change in mean score over 48 months in A. MDS-UPDRS part II score, B. PDQ-39 mobility subscale, and Montreal Cognitive Assessment (MoCA). Error bars represent standard error of the mean. There is no significant difference in symptom progression rate by levodopa formulation.

Table 1.

Baseline demographic and earliest available clinical data for the three groups and total population. All measures shown represent the median value unless otherwise specified as percentage. Disease duration was measured from the time of diagnosis of PD.

	IR	CR	CLE	ALL
N	152	53	28	233
Age at Baseline (IQR)	67.58 (10.83)	69.5 (10.5)	64.38 (10.85)	67.5 (11.17)
Disease Duration in years (IQR)	4.33 (5.17), n = 151	3.67 (4.33)	9.04 (6.73)	4.5 (5.58), n = 232
MDS-UPDRS				
Part I (IQR)	9 (7)	6 (5)	8.5 (8.25)	8 (7)
Part II (IQR)	7 (8)	5 (8)	10.5 (8.5)	7 (9)
Part III (IQR)	21 (17.75), n = 150	13 (6)	24 (26.25)	19 (18), n = 231
Part IV (IQR)	0.5 (4)	0 (2)	4 (7)	0 (4)
Total (IQR)	42 (27.75), n = 150	23 (14)	52.5 (36)	38 (29), n = 231
Site				
UT Southwestern (%)	47 (30.92)	53 (100)	10 (35.71)	110 (47.21)
Hershey Medical Center (%)	55 (36.18)	0 (0)	9 (32.14)	64 (27.47)
Johns Hopkins University (%)	50 (32.89)	0 (0)	9 (32.14)	59 (25.32)
Female (%)	62 (40.79)	18 (33.96)	14 (50)	94 (40.34)
Race				
Caucasian (%)	144 (94.74)	49 (92.45)	27 (96.43)	220 (94.42)
Asian (East) (%)	3 (1.97)	1 (1.89)	0 (0)	4 (1.72)
African American (%)	2 (1.32)	2 (3.77)	0 (0)	4 (1.72)
Asian (West) (%)	1 (0.66)	1 (1.89)	0 (0)	2 (0.86)
American Indian/Alaskan Native (%)	1 (0.66)	0 (0)	0 (0)	1 (0.43)
Unknown or Not Reported (%)	0 (0)	0 (0)	1 (3.57)	1 (0.43)
Hispanic (%)	1 (0.66)	0 (0)	0 (0)	1 (0.43)
Ethnicity				
Non-Hispanic/Latino (%)	132 (86.84)	50 (94.34)	22 (78.57)	204 (87.55)
Hispanic/Latino (%)	5 (3.29)	3 (5.66)	1 (3.57)	9 (3.86)
Not Reported (%)	14 (9.21)	0 (0)	5 (17.86)	19 (8.15)
Unknown (%)	1 (0.66)	0 (0)	0 (0)	1 (0.43)
Years of Education at Baseline (IQR)	16 (5), n = 151	18 (2)	16 (4.5)	16 (4), n = 232
Age at Diagnosis (IQR)	62 (13), n = 151	63 (13)	55 (11.5)	62 (12), n = 232
MoCA (IQR)	26 (4.5), n = 127	27 (3), n = 47	26 (3), n = 21	26 (4), n = 195
Schwab and England (IQR)	0.9 (0.1), n = 128	0.9 (0.1), n = 47	0.9 (0.1), n = 21	0.9 (0.1), n = 196
HAM-A (IQR)	6 (6), n = 151	4 (6)	7 (5.75)	5 (5), n = 232
HAM-D (IQR)	4 (5), n = 151	3 (4)	5 (6)	4 (5), n = 232
PDQ-39 Mobility (IQR)	7.5 (17.5), n = 127	2.5 (10), n = 47	7.5 (22.5), n = 21	5 (15), n = 195
LEDD (IQR)	600 (364.38)	565 (425)	997.62 (620.25)	600 (409)
Total IR Equivalent Daily Dosage (IQR)	400 (300)	225 (225)	773.06 (507.06)	400 (300)
Non-Levodopa LEDD (IQR)	150 (263.75)	180 (240)	340 (385)	175 (260)

IR=immediate-release carbidopa/levodopa, CR=controlled-release carbidopa/levodopa, CLE=carbidopa/levodopa/entacapone, MoCA=Montreal Cognitive Assessment, HAM-A=Hamilton Anxiety Scale, HAM-D=Hamilton Depression Scale, PDQ-39=Parkinson's Disease Questionnaire, LEDD=Levodopa equivalent daily dosage

Table 2.

Primary analyses showing annual progression by oral levodopa formulation. P-value adjustments were performed using the Sidák correction based on a total of 9 primary analyses performed.

	Difference in Estimated Annual Progression Rates[a]	Coefficient Estimate (95% Credible Interval)[b]	p-value[c]	Adjusted p-value
MDS-UPDRS Total Score[d]				
CR - IR	1.12 (−0.32, 2.56)	0.06 (0, 0.11)	0.0376	0.3384
CLE - IR	−0.32 (−2.23, 1.69)	0 (−0.07, 0.06)	0.8794	> 0.9999
CR - CLE	1.43 (−0.77, 3.54)	0.06 (−0.01, 0.13)	0.1094	0.9846
MDS-UPDRS Part II[e]				
CR - IR	−0.36 (−0.93, 0.18)	−0.04 (−0.14, 0.06)	0.4198	> 0.9999
CLE - IR	−0.26 (−0.91, 0.43)	−0.04 (−0.14, 0.07)	0.4646	> 0.9999
CR - CLE	−0.10 (−0.91, 0.63)	0 (−0.13, 0.13)	0.9992	> 0.9999
MDS-UPDRS Part IV[e]				
CR - IR	0.03 (−0.16, 0.22)	0.13 (−0.17, 0.44)	0.3962	> 0.9999
CLE - IR	−0.13 (−0.53, 0.18)	−0.13 (−0.43, 0.16)	0.3764	> 0.9999
CR - CLE	0.15 (−0.19, 0.60)	0.26 (−0.12, 0.64)	0.1746	> 0.9999

IR=immediate-release carbidopa/levodopa, CR=controlled-release carbidopa/levodopa, CLE=carbidopa/levodopa/entacapone

[a] Due to changes in progression rates based on the value of other covariates, the estimated difference in progression rates is computed comparing two subjects assuming enrollment at the same site (UT Southwestern Medical Center), equivalent baseline IR levodopa equivalent daily dosage (LEDD, 400 mg), and equivalent baseline LEDD for non-levodopa PD medications (160 mg), and assuming no change in the IR LEDD or non-levodopa PD medications over 48 months

[b] Coefficients are based on the log scale

[c] Two-sided Bayesian p-value

[d] Modeled using a mixed effects regression model based on the lognormal family function

[e] Modeled using a mixed effects regression model based on the negative binomial family function

Table 3.

Secondary analyses showing annual symptom progression rates. All p-values should be interpreted with caution due to the inflation of the Type I error rate due to multiple testing.

	Difference in Estimated Annual Progression Rates[a]	Coefficient Estimate (95% Credible Interval)[b]	p-value[c]
GCO[d]			
CR - IR	0.08 (0.02, 0.15)	0.08 (0.02, 0.15)	0.0130
CLE - IR	0.03 (−0.05, 0.12)	0.03 (−0.05, 0.12)	0.4216
CR - CLE	0.05 (−0.05, 0.14)	0.05 (−0.05, 0.14)	0.3104
LEDD[e]			
CR - IR	−14.85 (−52.21, 21.81)	−0.15 (−0.52, 0.22)	0.4358
CLE - IR	−17.14 (−60.25, 25.57)	−0.17 (−0.6, 0.26)	0.4230
CR - CLE	2.29 (−48.26, 52.93)	0.02 (−0.48, 0.53)	0.9448
	Difference in Estimated Annual Progression Rates[a]	**Coefficient Estimate (95% Credible Interval)[f]**	**p-value[c]**
MoCA[g]			
CR - IR	−0.03 (−0.40, 0.33)	−0.03 (−0.15, 0.09)	0.5904
CLE - IR	−0.16 (−0.68, 0.26)	0.01 (−0.12, 0.14)	0.8608
CR - CLE	0.13 (−0.40, 0.75)	−0.04 (−0.2, 0.12)	0.5882
PDQ-39 Mobility[g]			
CR - IR	−0.74 (−2.28, 0.53)	0.05 (−0.17, 0.27)	0.6352
CLE - IR	−1.31 (−3.30, 0.39)	−0.17 (−0.41, 0.08)	0.1762
CR - CLE	0.56 (−1.34, 2.41)	0.22 (−0.08, 0.51)	0.1510
	Difference in Annual Estimated Progression Rates[a]	**Coefficient Estimate (95% Credible Interval)[h]**	**p-value[c]**
Schwab and England[i]			
CR - IR	0 (0, 0)	−0.11 (−0.6, 0.39)	0.6372
CLE - IR	0 (0, 0)	−0.23 (−0.82, 0.34)	0.4380
CR - CLE	0 (0, 0)	0.12 (−0.56, 0.81)	0.7500

IR=immediate-release carbidopa/levodopa, CR=controlled-release carbidopa/levodopa, CLE=carbidopa/levodopa/entacapone, GCO=Global Composite Outcome, LEDD=Levodopa equivalent daily dosage, MoCA=Montreal Cognitive Assessment, PDQ-39=Parkinson's Disease Questionnaire.

[a] Due to changes in progression rates based on the value of other covariates, the estimated difference in progression rates is computed comparing two subjects assuming enrollment at the same site (UT Southwestern Medical Center), equivalent baseline IR levodopa equivalent daily dosage (LEDD, 400 mg), and equivalent baseline LEDD for non-levodopa PD medications (160 mg), and assuming no change in the IR LEDD or non-levodopa PD medications over 48 months

[b] Coefficients are not transformed from the original value of the progression measurement

[c] Two-sided Bayesian p-value

[d] Modeled using a mixed effects regression model based on the Student's *t* family function

[e] Modeled using a mixed effects regression model based on the Gaussian family function

[f] Coefficients are on the log scale

[g] Modeled using a mixed effects regression model based on the negative binomial family function

[h] Coefficients are on the logit scale

[i] Model using a cumulative logit mixed effects model