Clinical trial results:
A Study to Examine the Effect of Levodopa-Carbidopa Intestinal Gel (LCIG) Therapy Relative to That of Optimized Medical Treatment (OMT) on Non-motor Symptoms (NMS) Associated With Advanced Parkinson's Disease (PD)

Summary

EudraCT number	2014-004865-26
Trial protocol	DE SE IT ES GR
Global end of trial date	18 November 2022

Results information

Result version number	v1 (current)
This version publication date	22 November 2023
First version publication date	22 November 2023

Trial information

Trial identification

Sponsor protocol code	M12-927

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02549092
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AbbVie Deutschland GmbH & Co. KG
Sponsor organisation address	AbbVie House, Vanwall Business Park, Vanwall Road, Maidenhead, Berkshire, United Kingdom, SL6 4UB
Public contact	Global Medical Services, AbbVie, 001 8006339110, abbvieclinicaltrials@abbvie.com
Scientific contact	Global Medical Services, AbbVie, 001 8006339110, abbvieclinicaltrials@abbvie.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 November 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 November 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to examine the effect of LCIG relative to that of OMT on NMS associated with advanced PD as assessed by the Non-Motor Symptom Scale (NMSS) Total Score and the Modified Parkinson's Disease Sleep Scale (PDSS)-2 Total Score.

Protection of trial subjects:

Subject and/or legal guardian read and understood the information provided about the study and gave written permission.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 October 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Greece: 1
Country: Number of subjects enrolled	Italy: 21
Country: Number of subjects enrolled	Korea, Republic of: 16
Country: Number of subjects enrolled	Australia: 8
Country: Number of subjects enrolled	Spain: 26
Country: Number of subjects enrolled	Sweden: 3
Country: Number of subjects enrolled	United States: 9
Worldwide total number of subjects	89
EEA total number of subjects	52

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0

Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	27
From 65 to 84 years	62
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 32 sites in 9 countries.

After a 30- to 67-day Screening Period for required procedures, training, and medication stabilization, eligible participants were randomized to Optimized Medical Treatment (OMT) or Levodopa-Carbidopa Intestinal Gel (LCIG) for a 26-week Treatment Period.

Pre-assignment

Screening details:

Before Treatment Period Day 1, LCIG participants had a percutaneous endoscopic gastrostomy with a jejunal extension (PEG-J; with an initial, optional, temporary nasojejunal [NJ] tube placement to titrate the dose of LCIG prior to the PEG-J).

Period 1

Period 1 title	Treatment Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Optimized Medical Treatment

Arm description:

Participants randomized to continue OMT remained on their current optimized regimen (oral, sublingual or transdermal anti-PD medications and medications to treat NMS per Investigator discretion and/or in accordance with approved product label of the prescribed medications)
during the 26-week treatment phase. Changes to anti-PD and NMS medications are to remain stable and can only be made if medically indicated.

Participants in the United States or South Korea may have elected to enter an Extension/Transition follow-up period to receive an individually optimized LCIG dose (after NJ and/or PEG-J placement), in order to transition to commercially available LCIG.

Arm type	Optimized Medical Treatment

No investigational medicinal product assigned in this arm

Arm title	LCIG

Arm description:

Participants randomized to LCIG at an individually optimized dose, in accordance with the LCIG approved product label for countries participating in the study during the 26-week treatment phase. Changes to anti-PD and NMS medications were to remain stable and were only made if medically indicated.
The total daily dose of LCIG was composed of 3 components: (i) the morning dose, (ii) continuous maintenance infusion dose and (iii) extra doses. The continuous infusion was expected to run over a period of 16 consecutive hours each day.
Participants in the United States or South Korea may have elected to enter an Extension/Transition follow-up period to receive an individually optimized LCIG dose, in order to transition to commercially available LCIG.

Arm type	Experimental
Investigational medicinal product name	Duodopa
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Intestinal gel
Routes of administration	Gastroenteral use

Dosage and administration details:

The total daily dose of LCIG was composed of 3 components: (i) the morning dose, (ii) continuous maintenance infusion dose and (iii) extra doses. The continuous infusion was expected to run over a

period of 16 consecutive hours each day.

Number of subjects in period 1	Optimized Medical Treatment	LCIG
Started	44	45
Completed	41	38
Not completed	3	7
Consent withdrawn by subject	1	3
Adverse event	2	2
Lack of efficacy	-	2

Period 2

Period 2 title	Extension/Transition Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Optimized Medical Treatment

Arm description:

Participants randomized to continue OMT remained on their current optimized regimen (oral, sublingual or transdermal anti-PD medications and medications to treat NMS per Investigator discretion and/or in accordance with approved product label of the prescribed medications)
during the 26-week treatment phase. Changes to anti-PD and NMS medications are to remain stable and can only be made if medically indicated.

Participants in the United States or South Korea may have elected to enter an Extension/Transition follow-up period to receive an individually optimized LCIG dose (after NJ and/or PEG-J placement), in order to transition to commercially available LCIG.

Arm type	Optimized Medical Treatment

No investigational medicinal product assigned in this arm

Arm title	LCIG

Arm description:

Participants randomized to LCIG at an individually optimized dose, in accordance with the LCIG approved product label for countries participating in the study during the 26-week treatment phase. Changes to anti-PD and NMS medications were to remain stable and were only made if medically indicated.
The total daily dose of LCIG was composed of 3 components: (i) the morning dose, (ii) continuous maintenance infusion dose and (iii) extra doses. The continuous infusion was expected to run over a period of 16 consecutive hours each day.
Participants in the United States or South Korea may have elected to enter an Extension/Transition

follow-up period to receive an individually optimized LCIG dose, in order to transition to commercially available LCIG.

Arm type	Experimental
Investigational medicinal product name	Duodopa
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Intestinal gel
Routes of administration	Gastroenteral use

Dosage and administration details:

The total daily dose of LCIG was composed of 3 components: (i) the morning dose, (ii) continuous maintenance infusion dose and (iii) extra doses. The continuous infusion was expected to run over a period of 16 consecutive hours each day.

Number of subjects in period 2[1]	Optimized Medical Treatment	LCIG
Started	10	14
Transitioned to commercial LCIG	5	7 [2]
Completed	5	10
Not completed	5	4
Consent withdrawn by subject	-	1
Other, not specified	4	2
Adverse event	1	1

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Participants in the United States or South Korea may have elected to enter an Extension/Transition follow-up period.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This row applies to those subjects who transitioned to LCIG after entering the extension/transition period.

Baseline characteristics

Reporting groups

Reporting group title	Optimized Medical Treatment

Reporting group description:

Participants randomized to continue OMT remained on their current optimized regimen (oral, sublingual or transdermal anti-PD medications and medications to treat NMS per Investigator discretion and/or in accordance with approved product label of the prescribed medications)
during the 26-week treatment phase. Changes to anti-PD and NMS medications are to remain stable and can only be made if medically indicated.

Participants in the United States or South Korea may have elected to enter an Extension/Transition follow-up period to receive an individually optimized LCIG dose (after NJ and/or PEG-J placement), in order to transition to commercially available LCIG.

Reporting group title	LCIG

Reporting group description:

Participants randomized to LCIG at an individually optimized dose, in accordance with the LCIG approved product label for countries participating in the study during the 26-week treatment phase. Changes to anti-PD and NMS medications were to remain stable and were only made if medically indicated.
The total daily dose of LCIG was composed of 3 components: (i) the morning dose, (ii) continuous maintenance infusion dose and (iii) extra doses. The continuous infusion was expected to run over a period of 16 consecutive hours each day.
Participants in the United States or South Korea may have elected to enter an Extension/Transition follow-up period to receive an individually optimized LCIG dose, in order to transition to commercially available LCIG.

Reporting group values	Optimized Medical Treatment	LCIG	Total
Number of subjects	44	45	89
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	68.6	66.8	
standard deviation	± 6.20	± 7.34	-
Gender categorical Units: Subjects			
Female	20	16	36
Male	24	29	53
Race Units: Subjects			
White	35	36	71
Black	0	1	1
Asian	9	8	17
Ethnicity Units: Subjects			
Hispanic or Latino	9	8	17
Not Hispanic or Latino	35	37	72
Non-Motor Symptoms Scale (NMSS) Total Score			
The NMSS consists of 30 questions in 9 domains (cardiovascular/falls, sleep/fatigue, mood/cognition, perceptual problems/hallucinations, attention/memory, gastrointestinal (GI) tract, urinary, sexual function, miscellaneous). Score of each question is calculated by multiplying severity*frequency.			

Severity and frequency are rated using a scale ranging from 0 (none) to 3 (severe) for severity and from 1 (rarely) to 4 (very frequent) for frequency. Total score is the sum of 9 domains, and ranges from 0 to 360, with a lower value indicating a more desirable outcome.			
Units: score on a scale arithmetic mean standard deviation	±	±	-
Modified Parkinson's Disease Sleep Scale (PDSS-2) Total Score			
The PDSS-2 addresses PD-specific sleep disturbances such as restless leg syndrome (RLS), morning akinesia, pain, and sleep apnea. The frequency is assessed for the 15 sleep problems based on a 5-point Likert-type scale (ranging from 0 [never] to 4 [very often]). Scores are calculated for each of the 3 domains (motor symptoms at night, PD symptoms at night, and disturbed sleep) as well as a total score. The PDSS-2 domain scores range from 0 to 20 and the total score is a sum of the 3 domains and ranges from 0 to 60.			
Units: score on a scale arithmetic mean standard deviation	±	±	-

Subject analysis sets

Subject analysis set title	Intent-to-Treat Data Set: Optimized Medical Treatment
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All participants randomized to the OMT arm who received at least one dose of study drug. Participants with a baseline measurement are reported in this table.

Subject analysis set title	Intent-to-Treat Data Set: LCIG
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All participants randomized to LCIG arm who received at least one dose of study drug. Participants with a baseline measurement are reported in this table.

Reporting group values	Intent-to-Treat Data Set: Optimized Medical Treatment	Intent-to-Treat Data Set: LCIG	
Number of subjects	43	42	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	±	±	
Gender categorical Units: Subjects			
Female Male			
Race Units: Subjects			
White Black Asian			
Ethnicity Units: Subjects			
Hispanic or Latino Not Hispanic or Latino			

Non-Motor Symptoms Scale (NMSS) Total Score			
The NMSS consists of 30 questions in 9 domains (cardiovascular/falls, sleep/fatigue, mood/cognition, perceptual problems/hallucinations, attention/memory, gastrointestinal (GI) tract, urinary, sexual function, miscellaneous). Score of each question is calculated by multiplying severity*frequency. Severity and frequency are rated using a scale ranging from 0 (none) to 3 (severe) for severity and from 1 (rarely) to 4 (very frequent) for frequency. Total score is the sum of 9 domains, and ranges from 0 to 360, with a lower value indicating a more desirable outcome.			
Units: score on a scale			
arithmetic mean	112.4	99.7	
standard deviation	± 51.37	± 46.49	
Modified Parkinson's Disease Sleep Scale (PDSS-2) Total Score			
The PDSS-2 addresses PD-specific sleep disturbances such as restless leg syndrome (RLS), morning akinesia, pain, and sleep apnea. The frequency is assessed for the 15 sleep problems based on a 5-point Likert-type scale (ranging from 0 [never] to 4 [very often]). Scores are calculated for each of the 3 domains (motor symptoms at night, PD symptoms at night, and disturbed sleep) as well as a total score. The PDSS-2 domain scores range from 0 to 20 and the total score is a sum of the 3 domains and ranges from 0 to 60.			
Units: score on a scale			
arithmetic mean	30.3	29.9	
standard deviation	± 8.55	± 7.36	

End points

End points reporting groups

Reporting group title	Optimized Medical Treatment

Reporting group description:

Participants randomized to continue OMT remained on their current optimized regimen (oral, sublingual or transdermal anti-PD medications and medications to treat NMS per Investigator discretion and/or in accordance with approved product label of the prescribed medications)
during the 26-week treatment phase. Changes to anti-PD and NMS medications are to remain stable and can only be made if medically indicated.

Participants in the United States or South Korea may have elected to enter an Extension/Transition follow-up period to receive an individually optimized LCIG dose (after NJ and/or PEG-J placement), in order to transition to commercially available LCIG.

Reporting group title	LCIG

Reporting group description:

Participants randomized to LCIG at an individually optimized dose, in accordance with the LCIG approved product label for countries participating in the study during the 26-week treatment phase. Changes to anti-PD and NMS medications were to remain stable and were only made if medically indicated.
The total daily dose of LCIG was composed of 3 components: (i) the morning dose, (ii) continuous maintenance infusion dose and (iii) extra doses. The continuous infusion was expected to run over a period of 16 consecutive hours each day.
Participants in the United States or South Korea may have elected to enter an Extension/Transition follow-up period to receive an individually optimized LCIG dose, in order to transition to commercially available LCIG.

Reporting group title	Optimized Medical Treatment

Reporting group description:

Participants randomized to continue OMT remained on their current optimized regimen (oral, sublingual or transdermal anti-PD medications and medications to treat NMS per Investigator discretion and/or in accordance with approved product label of the prescribed medications)
during the 26-week treatment phase. Changes to anti-PD and NMS medications are to remain stable and can only be made if medically indicated.

Participants in the United States or South Korea may have elected to enter an Extension/Transition follow-up period to receive an individually optimized LCIG dose (after NJ and/or PEG-J placement), in order to transition to commercially available LCIG.

Reporting group title	LCIG

Reporting group description:

Participants randomized to LCIG at an individually optimized dose, in accordance with the LCIG approved product label for countries participating in the study during the 26-week treatment phase. Changes to anti-PD and NMS medications were to remain stable and were only made if medically indicated.
The total daily dose of LCIG was composed of 3 components: (i) the morning dose, (ii) continuous maintenance infusion dose and (iii) extra doses. The continuous infusion was expected to run over a period of 16 consecutive hours each day.
Participants in the United States or South Korea may have elected to enter an Extension/Transition follow-up period to receive an individually optimized LCIG dose, in order to transition to commercially available LCIG.

Subject analysis set title	Intent-to-Treat Data Set: Optimized Medical Treatment
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All participants randomized to the OMT arm who received at least one dose of study drug. Participants with a baseline measurement are reported in this table.

Subject analysis set title	Intent-to-Treat Data Set: LCIG
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All participants randomized to LCIG arm who received at least one dose of study drug. Participants with a baseline measurement are reported in this table.

Primary: Change From Baseline to Week 26 in the NMSS Total Score

End point title	Change From Baseline to Week 26 in the NMSS Total Score

End point description:

The NMSS consists of 30 questions in 9 domains (cardiovascular/falls, sleep/fatigue, mood/cognition, perceptual problems/hallucinations, attention/memory, GI tract, urinary, sexual function, miscellaneous). Score of each question is calculated by multiplying severity*frequency. Severity and frequency are rated using a scale ranging from 0 (none) to 3 (severe) for severity and from 1 (rarely) to 4 (very frequent) for frequency. Total score is the sum of 9 domains, and ranges from 0 to 360, with a lower value indicating a more desirable outcome. Repeated-measure analysis.

Intent-to-Treat Data Set: all participants who were randomized to the OMT arm, and all participants who were randomized to LCIG arm and received at least one dose of study drug. Participants with baseline and a post-baseline measurement are reported in this table.

End point type	Primary

End point timeframe:

Baseline, Week 26

End point values	Optimized Medical Treatment	LCIG		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	42		
Units: score on a scale				
least squares mean (standard error)	-23.83 (± 8.30)	-32.04 (± 8.53)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Difference of LCIG - OMT

Comparison groups	Optimized Medical Treatment v LCIG
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.41 [2]
Method	mixed model repeated measures
Parameter estimate	Least Squares (LS) Mean of Difference
Point estimate	-8.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-27.98
upper limit	11.55
Variability estimate	Standard error of the mean
Dispersion value	9.91

Notes:

[1] - Adjusted for multiplicity using the Hochberg procedure to control the family-wise error rate at a pre-specified significance level (alpha = 0.05).

[2] - P value is from the mixed model repeated measures (MMRM) with the model: change from Baseline=treatment, country, visit, Baseline, treatment-by-visit, and Baseline-by-visit. Unstructured variance-covariance structure was used in the MMRM analysis.

Primary: Change From Baseline to Week 26 in the Modified PDSS-2 Total Score

End point title	Change From Baseline to Week 26 in the Modified PDSS-2 Total Score

End point description:

The PDSS-2 addresses PD-specific sleep disturbances such as restless leg syndrome (RLS), morning akinesia, pain, and sleep apnea. The frequency is assessed for the 15 sleep problems based on a 5-point Likert-type scale (ranging from 0 [never] to 4 [very often]). Scores are calculated for each of the 3 domains (motor symptoms at night, PD symptoms at night, and disturbed sleep) as well as a total score. The PDSS-2 domain scores range from 0 to 20 and the total score is a sum of the 3 domains and ranges from 0 to 60. Repeated measure analysis.

Intent-to-Treat Data Set: all participants who were randomized to the OMT arm, and all participants who were randomized to LCIG arm and received at least one dose of study drug. Participants with baseline and a post-baseline measurement are reported in this table.

End point type	Primary

End point timeframe:

Baseline, Week 26

End point values	Optimized Medical Treatment	LCIG		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	42		
Units: score on a scale				
least squares mean (standard error)	-8.98 (± 2.00)	-7.41 (± 2.01)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Difference of LCIG - OMT	
Comparison groups	Optimized Medical Treatment v LCIG
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.509 [4]
Method	mixed model repeated measures
Parameter estimate	LS Mean of Difference
Point estimate	1.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.16
upper limit	6.3
Variability estimate	Standard error of the mean
Dispersion value	2.37

Notes:

[3] - Adjusted for multiplicity using the Hochberg procedure to control the family-wise error rate at a pre-specified significance level (alpha = 0.05).
[4] - The P value is from the MMRM with the model: change from Baseline = treatment, country, visit, Baseline, treatment-by-visit, and Baseline-by-visit. The unstructured variance covariance structure was used in the MMRM analysis.

Secondary: Change From Baseline to Week 26 in Parkinson's Disease Questionnaire (PDQ-8) Summary Index Score

End point title	Change From Baseline to Week 26 in Parkinson's Disease Questionnaire (PDQ-8) Summary Index Score

End point description:

The PDQ-8 is a disease-specific instrument designed to measure aspects of health relevant to PD. Eight questions including the mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication, and bodily discomfort are assessed on a 5-point scale: 0 = Never, 1 = Occasionally, 2 = Sometimes, 3 = Often, 4 = Always (or cannot do at all, if applicable). Summary index score is the sum of each question divided by 32 and multiplied by 100. Scores range from 0 to 100 with lower values desirable.

Intent-to-Treat Data Set: all participants who were randomized to the OMT arm, and all participants who were randomized to LCIG arm and received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Optimized Medical Treatment	LCIG		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	43		
Units: score on a scale				
least squares mean (standard error)	-1.75 (± 2.96)	-5.56 (± 2.97)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Statistical significance for the 3 key secondary efficacy endpoints (PDQ-8 index score, CGI-C score, and UPDRS Part II) could only be evaluated using the Hochberg procedure for multiplicity control if both primary endpoints had been statistically significant after multiplicity adjustment.

Comparison groups	Optimized Medical Treatment v LCIG
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.291 [6]
Method	Repeated measures model
Parameter estimate	LS mean difference
Point estimate	-3.81

Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.96
upper limit	3.34
Variability estimate	Standard error of the mean
Dispersion value	3.59

Notes:

[5] - Difference of LCIG - OMT

[6] - The repeated measures model: change = treatment, country, visit, baseline, treatment * visit, baseline * visit. The unstructured variance-covariance structure is used.

Secondary: Clinical Global Impression of Change (CGI-C) Final Score

End point title	Clinical Global Impression of Change (CGI-C) Final Score

End point description:

CGI-C score is a clinician's impression of a subject's change in status on a 7-point scale (1 = very much improved, 2 = much improved, 3 = minimally Improved, 4 = no change, 5 = minimally worse, 6 = much worse, 7 = very much worse). Scores range from 1 to 7, with lower score desirable.

Intent-to-Treat Data Set: all participants who were randomized to the OMT arm, and all participants who were randomized to LCIG arm and received at least one dose of study drug. Participants with an assessment are reported in this table.

End point type	Secondary

End point timeframe:

End of Treatment Period (up to Week 26)

End point values	Optimized Medical Treatment	LCIG		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	40		
Units: score on a scale				
least squares mean (standard error)	4.9 (± 0.25)	2.5 (± 0.24)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Statistical significance for the 3 key secondary efficacy endpoints (PDQ-8 index score, CGI-C score, and UPDRS Part II) could only be evaluated using the Hochberg procedure for multiplicity control if both primary endpoints had been statistically significant after multiplicity adjustment.

Comparison groups	Optimized Medical Treatment v LCIG
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	< 0.001 [8]
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-2.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.84
upper limit	-1.82
Variability estimate	Standard error of the mean
Dispersion value	0.26

Notes:

[7] - Difference of LCIG - OMT

[8] - Analysis of covariance (ANCOVA) model: FINAL = treatment, country.

Secondary: Change From Baseline at Week 26 in Unified Parkinson's Disease Rating Scale (UPDRS) Part II Score

End point title	Change From Baseline at Week 26 in Unified Parkinson's Disease Rating Scale (UPDRS) Part II Score

End point description:

UPDRS is an investigator-used rating tool to follow the longitudinal course of Parkinson's disease of 42 total questions. Part I (Questions 1 – 4), Part II (Questions 5 – 17), Part III (Questions 18 – 31), and Part IV (Questions 32 – 42). Questions 35 – 38 and 40 – 42 are 2-point (0 and 1), all other questions are 5-point (0 – 4). Part II scores range from 0 to 52 with lower value desirable.

Intent-to-Treat Data Set: all participants who were randomized to the OMT arm, and all participants who were randomized to LCIG arm and received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Optimized Medical Treatment	LCIG		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	43		
Units: score on a scale				
least squares mean (standard error)	0.53 (± 0.89)	-2.26 (± 0.87)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Statistical significance for the 3 key secondary efficacy endpoints (PDQ-8 index score, CGI-C score, and UPDRS Part II) could only be evaluated using the Hochberg procedure for multiplicity control if both primary endpoints had been statistically significant after multiplicity adjustment.

Comparison groups	Optimized Medical Treatment v LCIG
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.006 [10]
Method	Repeated measures model
Parameter estimate	LS mean difference
Point estimate	-2.79

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.77
upper limit	-0.81
Variability estimate	Standard error of the mean
Dispersion value	0.99

Notes:

[9] - Difference of LCIG - OMT

[10] - The repeated measures model: change = treatment, country, visit, baseline, treatment * visit, baseline * visit. The unstructured variance-covariance structure is used.

Secondary: Change From Baseline to Week 26 in the NMSS Domain Scores

End point title	Change From Baseline to Week 26 in the NMSS Domain Scores

End point description:

The NMSS consists of 30 questions in 9 domains. Score is calculated by multiplying severity*frequency. Severity and frequency are rated using a scale of 0 (none) to 3 (severe) for severity and 1 (rarely) to 4 (very frequent) for frequency, with lower values desirable for each score. Cardiovascular/falls scores range from 0-24. Sleep/fatigue scores range from 0-48. Mood/cognition scores range from 0-72. Perceptual problems/hallucinations scores range from 0-36. Attention/memory scores range from 0-36. Gastrointestinal tract scores range from 0-36. Urinary scores range from 0-36. Sexual function scores range from 0-24. Miscellaneous scores range from 0-48. Repeated measure analysis.

Intent-to-Treat Data Set: all participants who were randomized to the OMT arm, and all participants who were randomized to LCIG arm and received at least one dose of study drug. Participants with baseline and a post-baseline measurement are reported in this table.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Optimized Medical Treatment	LCIG		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	42		
Units: score on a scale				
least squares mean (standard error)				
Cardiovascular including falls	-1.84 (± 0.82)	-1.76 (± 0.86)		
Sleep/fatigue	-7.11 (± 2.02)	-6.06 (± 2.06)		
Mood/cognition	-5.99 (± 3.06)	-7.84 (± 3.11)		
Perceptual problems/hallucinations	-1.53 (± 0.70)	-1.14 (± 0.72)		
Attention/memory	-1.20 (± 1.60)	-2.15 (± 1.66)		
Gastrointestinal tract	-0.85 (± 1.09)	-3.43 (± 1.14)		
Urinary	-3.65 (± 1.90)	-4.83 (± 1.96)		
Sexual function	0.88 (± 0.86)	0.10 (± 0.90)		
Miscellaneous	-3.87 (± 1.53)	-5.16 (± 1.60)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Cardiovascular including falls	
Comparison groups	Optimized Medical Treatment v LCIG
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	= 0.933 [12]
Method	Repeated measures model
Parameter estimate	LS mean difference
Point estimate	0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.89
upper limit	2.06
Variability estimate	Standard error of the mean
Dispersion value	0.99

Notes:

[11] - Difference of LCIG - OMT

[12] - The repeated measures model: change = treatment, country, visit, baseline, treatment * visit, baseline * visit. The unstructured variance-covariance structure is used.

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Sleep/fatigue	
Comparison groups	Optimized Medical Treatment v LCIG
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	= 0.655 [14]
Method	Repeated measures model
Parameter estimate	LS mean difference
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.63
upper limit	5.74
Variability estimate	Standard error of the mean
Dispersion value	2.35

Notes:

[13] - Difference of LCIG - OMT

[14] - The repeated measures model: change = treatment, country, visit, baseline, treatment * visit, baseline * visit. The unstructured variance-covariance structure is used.

Statistical analysis title	Statistical Analysis 3
Statistical analysis description:	
Mood/cognition	
Comparison groups	Optimized Medical Treatment v LCIG

Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	= 0.616 [16]
Method	Repeated measures model
Parameter estimate	LS mean difference
Point estimate	-1.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.18
upper limit	5.48
Variability estimate	Standard error of the mean
Dispersion value	3.67

Notes:

[15] - Difference of LCIG - OMT

[16] - The repeated measures model: change = treatment, country, visit, baseline, treatment * visit, baseline * visit. The unstructured variance-covariance structure is used.

Statistical analysis title	Statistical Analysis 4

Statistical analysis description:

Perceptual problems/hallucinations

Comparison groups	Optimized Medical Treatment v LCIG
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	= 0.645 [18]
Method	Repeated measures model
Parameter estimate	LS mean difference
Point estimate	0.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	2.08
Variability estimate	Standard error of the mean
Dispersion value	0.84

Notes:

[17] - Difference of LCIG - OMT

[18] - The repeated measures model: change = treatment, country, visit, baseline, treatment * visit, baseline * visit. The unstructured variance-covariance structure is used.

Statistical analysis title	Statistical Analysis 5

Statistical analysis description:

Attention/memory

Comparison groups	Optimized Medical Treatment v LCIG
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	= 0.645 [20]
Method	Repeated measures model
Parameter estimate	LS mean difference
Point estimate	-0.94

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.03
upper limit	3.14
Variability estimate	Standard error of the mean
Dispersion value	2.04

Notes:

[19] - Difference of LCIG - OMT

[20] - The repeated measures model: change = treatment, country, visit, baseline, treatment * visit, baseline * visit. The unstructured variance-covariance structure is used.

Statistical analysis title	Statistical Analysis 6

Statistical analysis description:

Gastrointestinal tract

Comparison groups	Optimized Medical Treatment v LCIG
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority[21]
P-value	= 0.058 [22]
Method	Repeated measures model
Parameter estimate	LS mean difference
Point estimate	-2.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.25
upper limit	0.09
Variability estimate	Standard error of the mean
Dispersion value	1.34

Notes:

[21] - Difference of LCIG - OMT

[22] - The repeated measures model: change = treatment, country, visit, baseline, treatment * visit, baseline * visit. The unstructured variance-covariance structure is used.

Statistical analysis title	Statistical Analysis 7

Statistical analysis description:

Urinary

Comparison groups	Optimized Medical Treatment v LCIG
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority[23]
P-value	= 0.588 [24]
Method	Repeated measures model
Parameter estimate	LS mean difference
Point estimate	-1.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.52
upper limit	3.15
Variability estimate	Standard error of the mean
Dispersion value	2.17

Notes:

[23] - Difference of LCIG - OMT

[24] - The repeated measures model: change = treatment, country, visit, baseline, treatment * visit, baseline * visit. The unstructured variance-covariance structure is used.

Statistical analysis title	Statistical Analysis 8

Statistical analysis description:

Sexual function

Comparison groups	Optimized Medical Treatment v LCIG
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority[25]
P-value	= 0.464 [26]
Method	Repeated measures model
Parameter estimate	LS mean difference
Point estimate	-0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.88
upper limit	1.33
Variability estimate	Standard error of the mean
Dispersion value	1.05

Notes:

[25] - Difference of LCIG - OMT

[26] - The repeated measures model: change = treatment, country, visit, baseline, treatment * visit, baseline * visit. The unstructured variance-covariance structure is used.

Statistical analysis title	Statistical Analysis 9

Statistical analysis description:

Miscellaneous

Comparison groups	Optimized Medical Treatment v LCIG
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority[27]
P-value	= 0.468 [28]
Method	Repeated measures model
Parameter estimate	LS mean difference
Point estimate	-1.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.8
upper limit	2.23
Variability estimate	Standard error of the mean
Dispersion value	1.76

Notes:

[27] - Difference of LCIG - OMT

[28] - The repeated measures model: change = treatment, country, visit, baseline, treatment * visit, baseline * visit. The unstructured variance-covariance structure is used.

Secondary: Change From Baseline to Week 26 in the Modified PDSS-2 Domain

Scores

End point title	Change From Baseline to Week 26 in the Modified PDSS-2 Domain Scores

End point description:

The PDSS-2 addresses PD-specific sleep disturbances such as restless leg syndrome (RLS), morning akinesia, pain, and sleep apnea. The frequency is assessed for the 15 sleep problems based on a 5-point Likert-type scale (ranging from 0 [never] to 4 [very often]). Scores are calculated for each of the 3 domains (motor symptoms at night, PD symptoms at night, and disturbed sleep) as well as a total score. The PDSS-2 domain scores range from 0 to 20 and the total score is a sum of the 3 domains and ranges from 0 to 60. Repeated measure analysis.

Intent-to-Treat Data Set: all participants who were randomized to the OMT arm, and all participants who were randomized to LCIG arm and received at least one dose of study drug. Participants with baseline and a post-baseline measurement are reported in this table.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Optimized Medical Treatment	LCIG		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	42		
Units: score on a scale				
least squares mean (standard error)				
Motor symptoms at night	-2.21 (± 1.04)	-2.79 (± 1.05)		
PD symptoms at night	-1.77 (± 0.66)	-1.53 (± 0.69)		
Disturbed sleep	-4.88 (± 0.74)	-2.89 (± 0.75)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Motor symptoms at night

Comparison groups	Optimized Medical Treatment v LCIG
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority[29]
P-value	= 0.643 [30]
Method	repeated measures model
Parameter estimate	LS Method of Mean of Difference
Point estimate	-0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.09
upper limit	1.92

Variability estimate	Standard error of the mean
Dispersion value	1.26

Notes:

[29] - Difference of LCIG - OMT

[30] - The repeated measures model: change = treatment, country, visit, baseline, treatment * visit, baseline * visit. The unstructured variance-covariance structure is used.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

PD symptoms at night

Comparison groups	Optimized Medical Treatment v LCIG
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority[31]
P-value	= 0.769 [32]
Method	repeated measures model
Parameter estimate	LS Method of Mean of Difference
Point estimate	0.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.39
upper limit	1.87
Variability estimate	Standard error of the mean
Dispersion value	0.82

Notes:

[31] - Difference of LCIG - OMT

[32] - The repeated measures model: change = treatment, country, visit, baseline, treatment * visit, baseline * visit. The unstructured variance-covariance structure is used.

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Disturbed sleep

Comparison groups	Optimized Medical Treatment v LCIG
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority[33]
P-value	= 0.02 [34]
Method	repeated measures model
Parameter estimate	LS Method of Mean of Difference
Point estimate	1.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.32
upper limit	3.66
Variability estimate	Standard error of the mean
Dispersion value	0.84

Notes:

[33] - Difference of LCIG - OMT

[34] - The repeated measures model: change = treatment, country, visit, baseline, treatment * visit, baseline * visit. The unstructured variance-covariance structure is used.

Secondary: Change From Baseline at Week 26 in UPDRS Parts I, III, and IV Score

End point title	Change From Baseline at Week 26 in UPDRS Parts I, III, and IV Score

End point description:

UPDRS is an investigator-used rating tool to follow the longitudinal course of Parkinson's disease of 42 total questions. Part I (Questions 1 – 4), Part II (Questions 5 – 17), Part III (Questions 18 – 31), and Part IV (Questions 32 – 42). Questions 35 – 38 and 40 – 42 are 2-point (0 and 1), all other questions are 5-point (0 – 4). Part I is the sum of Questions 1 – 4; scores range from 0 to 16 with lower value desirable. Part III is the sum of Questions 18 – 31 (Questions 20 – 26 apply to multiple body parts, resulting in 27 answers total); scores range from 0 to 108 with lower value desirable. Part IV is the sum of Questions 32 – 42; scores range from 0 to 23 with lower value desirable.

Intent-to-Treat Data Set: all participants who were randomized to the OMT arm, and all participants who were randomized to LCIG arm and received at least one dose of study drug. Participants with baseline and a post-baseline measurement are reported in this table.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Optimized Medical Treatment	LCIG		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44[35]	43[36]		
Units: score on a scale				
least squares mean (standard error)				
Part I; n=44, 43	0.20 (± 0.39)	0.39 (± 0.39)		
Part III; n=43, 43	1.32 (± 1.84)	-0.89 (± 1.80)		
Part IV; n=44, 43	-0.61 (± 0.53)	-2.31 (± 0.52)		

Notes:

[35] - n=participants with an assessment

[36] - n=participants with an assessment

Attachments (see zip file)	Statistical Analyses_Change From Baseline at Week 26 in

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline at Week 26 in Parkinson's Anxiety Scale (PAS) Total Score

End point title	Change From Baseline at Week 26 in Parkinson's Anxiety Scale (PAS) Total Score

End point description:

PAS is a 12-item scale developed specifically to measure severity in anxiety in Parkinson's disease for the following items: Feeling anxious or nervous; Feeling tense or stressed; Being unable to relax; Excessive worrying about everyday matters; Fear of something bad, or even the worst, happening; Panic or intense fear; Shortness of breath; Heart palpitations or heart beating fast; Fear of losing control; Social situations; Public settings; Specific objects or situations. Severity for each item is rated as: 0, Never; 1 Rarely; 2, Sometimes; 3, Often; 4, Nearly always. Total score is the sum of the12 item scores, with a range of 0 to 48; a lower value is desirable.

Intent-to-Treat Data Set: all participants who were randomized to the OMT arm, and all participants who were randomized to LCIG arm and received at least one dose of study drug. Participants with baseline and a post-baseline measurement are reported in this table.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Optimized Medical Treatment	LCIG		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	41		
Units: score on a scale				
least squares mean (standard error)	-0.75 (± 1.28)	-2.29 (± 1.27)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Optimized Medical Treatment v LCIG
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority[37]
P-value	= 0.307 [38]
Method	repeated measures model
Parameter estimate	LS Mean of Difference
Point estimate	-1.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.52
upper limit	1.44
Variability estimate	Standard error of the mean
Dispersion value	1.5

Notes:

[37] - Difference of LCIG - OMT

[38] - The repeated measures model: change = treatment, country, visit, baseline, treatment * visit, baseline * visit. The unstructured variance-covariance structure is used.

Secondary: Change From Baseline at Week 26 in Geriatric Depression Scale (GDS-15) Score

End point title	Change From Baseline at Week 26 in Geriatric Depression Scale (GDS-15) Score

End point description:

The GDS-15 is a screening instrument for depression in the elderly of 15 yes/no questions: 1) Satisfied with life 2) Dropped many activities and interests 3) Life is empty 4) Often get bored 5) In good spirits most of the time 6) Afraid that something bad is going to happen 7) Feel happy most of the time 8) Often feel helpless 9) Prefer to stay at home, rather than going out and doing things 10) Feel that have more problems with memory than most 11) Think it is wonderful to be alive now 12) Feel worthless 13) Feel full of energy 14) Situation is hopeless 15) Most subjects are better off. Answers of 'yes' to questions 2, 3, 4, 6, 8, 9, 10, 12, 14, 15 are scored 1 point. Answers of 'no' to questions 1, 5, 7, 11, 13 are scored 1 point. The 15 items are summed and scores range from 0-15 with lower value desirable.

Intent-to-Treat Data Set: all participants randomized to the OMT arm, and all participants randomized to LCIG arm and received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Optimized Medical Treatment	LCIG		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	43		
Units: score on a scale				
least squares mean (standard error)	0.25 (± 0.40)	0.17 (± 0.39)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Optimized Medical Treatment v LCIG
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority[39]
P-value	= 0.868 [40]
Method	repeated measures model
Parameter estimate	LS Mean of Difference
Point estimate	-0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.99
upper limit	0.84
Variability estimate	Standard error of the mean
Dispersion value	0.46

Notes:

[39] - Difference of LCIG - OMT

[40] - The repeated measures model: change = treatment, country, visit, baseline, treatment * visit, baseline * visit. The unstructured variance-covariance structure is used.

Secondary: Change From Baseline at Week 26 in King's PD Pain Scale (KPPS) Score

End point title	Change From Baseline at Week 26 in King's PD Pain Scale (KPPS) Score

End point description:

The KPPS score is a clinical PD-specific pain scale of 14 items addressing the following 7 domains: musculoskeletal pain, chronic pain, fluctuation-related pain, nocturnal pain, orofacial pain, neuropathic pain, radicular pain. Each domain item is scored by severity (0, none to 3, very severe) multiplied by frequency (0, never to 4, all the time) resulting in a subscore of 0 – 12 (with lower value desirable), the sum of the 14 items gives the total score with a range from 0 to 168 with lower value desirable.

Intent-to-Treat Data Set: all participants who were randomized to the OMT arm, and all participants who were randomized to LCIG arm and received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Optimized Medical Treatment	LCIG		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	43		
Units: score on a scale				
least squares mean (standard error)				
Total score	-11.32 (± 2.83)	-12.46 (± 2.77)		
Musculoskeletal Pain Score	-1.72 (± 0.63)	-1.79 (± 0.62)		
Chronic pain score	-0.84 (± 0.54)	-0.77 (± 0.55)		
Fluctuation related pain score	-3.77 (± 1.30)	-3.14 (± 1.28)		
Nocturnal pain score	-2.41 (± 1.04)	-2.78 (± 1.01)		
Orofacial pain score	-0.74 (± 0.41)	-0.87 (± 0.41)		
Discoloration and edema score	-0.47 (± 0.65)	-2.27 (± 0.65)		
Radicular pain score	-1.43 (± 0.39)	-1.47 (± 0.39)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Total score	
Comparison groups	Optimized Medical Treatment v LCIG
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority[41]
P-value	= 0.728 [42]
Method	repeated measures model
Parameter estimate	LS Mean of Difference
Point estimate	-1.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.68
upper limit	5.39
Variability estimate	Standard error of the mean
Dispersion value	3.28

Notes:

[41] - Difference of LCIG - OMT

[42] - The repeated measures model: change = treatment, country, visit, baseline, treatment * visit, baseline * visit. The unstructured variance-covariance structure is used.

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Musculoskeletal pain score	
Comparison groups	Optimized Medical Treatment v LCIG

Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority[43]
P-value	= 0.916 [44]
Method	repeated measures model
Parameter estimate	LS Mean of Difference
Point estimate	-0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	1.35
Variability estimate	Standard error of the mean
Dispersion value	0.71

Notes:

[43] - Difference of LCIG - OMT

[44] - The repeated measures model: change = treatment, country, visit, baseline, treatment * visit, baseline * visit. The unstructured variance-covariance structure is used.

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Chronic pain score

Comparison groups	Optimized Medical Treatment v LCIG
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority[45]
P-value	= 0.919 [46]
Method	repeated measures model
Parameter estimate	LS Mean of Difference
Point estimate	0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.28
upper limit	1.42
Variability estimate	Standard error of the mean
Dispersion value	0.68

Notes:

[45] - Difference of LCIG - OMT

[46] - The repeated measures model: change = treatment, country, visit, baseline, treatment * visit, baseline * visit. The unstructured variance-covariance structure is used.

Statistical analysis title	Statistical Analysis 4

Statistical analysis description:

Fluctuation related pain score

Comparison groups	Optimized Medical Treatment v LCIG
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority[47]
P-value	= 0.68 [48]
Method	repeated measures model
Parameter estimate	LS Mean of Difference
Point estimate	0.63

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.42
upper limit	3.68
Variability estimate	Standard error of the mean
Dispersion value	1.53

Notes:

[47] - Difference of LCIG - OMT

[48] - The repeated measures model: change = treatment, country, visit, baseline, treatment * visit, baseline * visit. The unstructured variance-covariance structure is used.

Statistical analysis title	Statistical Analysis 5

Statistical analysis description:

Nocturnal pain score

Comparison groups	Optimized Medical Treatment v LCIG
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority[49]
P-value	= 0.767 [50]
Method	repeated measures model
Parameter estimate	LS Mean of Difference
Point estimate	-0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.83
upper limit	2.09
Variability estimate	Standard error of the mean
Dispersion value	1.24

Notes:

[49] - Difference of LCIG - OMT

[50] - The repeated measures model: change = treatment, country, visit, baseline, treatment * visit, baseline * visit. The unstructured variance-covariance structure is used.

Statistical analysis title	Statistical Analysis 6

Statistical analysis description:

Orofacial pain score

Comparison groups	Optimized Medical Treatment v LCIG
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority[51]
P-value	= 0.804 [52]
Method	repeated measures model
Parameter estimate	LS Mean of Difference
Point estimate	-0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.15
upper limit	0.9
Variability estimate	Standard error of the mean
Dispersion value	0.51

Notes:

[51] - Difference of LCIG - OMT

[52] - The repeated measures model: change = treatment, country, visit, baseline, treatment * visit, baseline * visit. The unstructured variance-covariance structure is used.

Statistical analysis title	Statistical Analysis 7
Statistical analysis description:	
Discoloration and edema score	
Comparison groups	Optimized Medical Treatment v LCIG
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority[53]
P-value	= 0.025 [54]
Method	repeated measures model
Parameter estimate	LS Mean of Difference
Point estimate	-1.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.38
upper limit	-0.23
Variability estimate	Standard error of the mean
Dispersion value	0.79

Notes:

[53] - Difference of LCIG - OMT

[54] - The repeated measures model: change = treatment, country, visit, baseline, treatment * visit, baseline * visit. The unstructured variance-covariance structure is used.

Statistical analysis title	Statistical Analysis 8
Statistical analysis description:	
Radicular pain score	
Comparison groups	Optimized Medical Treatment v LCIG
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority[55]
P-value	= 0.93 [56]
Method	repeated measures model
Parameter estimate	LS Mean of Difference
Point estimate	-0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.99
upper limit	0.9
Variability estimate	Standard error of the mean
Dispersion value	0.47

Notes:

[55] - Difference of LCIG - OMT

[56] - The repeated measures model: change = treatment, country, visit, baseline, treatment * visit, baseline * visit. The unstructured variance-covariance structure is used.

Secondary: Patient Global Impression of Change (PGIC) Final Score

End point title	Patient Global Impression of Change (PGIC) Final Score

End point description:

The PGIC is a 7-point response scale. The participant was asked by the Investigator or qualified designee to rate their change in status using the following 7-point scale: 1 = Very much improved, 2 = Much improved, 3 = Minimally improved, 4 = No change, 5 = Minimally worse, 6 = Much worse, 7 = Very much worse. PGIC score ranges from 1 to 7 with lower score desirable.

Intent-to-Treat Data Set: all participants who were randomized to the OMT arm, and all participants who were randomized to LCIG arm and received at least one dose of study drug. Participants with an assessment are reported in this table.

End point type	Secondary

End point timeframe:

End of Treatment Period (up to Week 26)

End point values	Optimized Medical Treatment	LCIG		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	40		
Units: score on a scale				
least squares mean (standard error)	4.9 (± 0.25)	2.5 (± 0.24)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Optimized Medical Treatment v LCIG
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	superiority[57]
P-value	< 0.001 [58]
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.89
upper limit	-1.87
Variability estimate	Standard error of the mean
Dispersion value	0.26

Notes:

[57] - Difference of LCIG - OMT

[58] - ANCOVA model: FINAL = treatment, country.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events are reported from the time of randomization until 30 days following last OMT dose, last study visit, discontinuation of study drug administration, removal of the PEG-J tube or Last LCIG Commercial Transition Visit have elapsed.

Adverse event reporting additional description:

Median duration of follow-up was 191 days for OMT and 565 days for LCIG in the Treatment Period, and was 1366 days for OMT -> LCIG and 1003.5 days for LCIG -> LCIG in the Extension/Transition period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Optimized Medical Treatment (OMT)

Reporting group description:

Participants randomized to continue OMT remained on their current optimized regimen during the 26-week treatment phase. Changes to anti-PD and NMS medications are to remain stable and can only be made if medically indicated.

Reporting group title	Extension/Transition LCIG ->LCIG

Reporting group description:

Participants randomized to LCIG in the United States or South Korea who elected to enter an Extension/ Transition follow-up period to receive an individually optimized LCIG dose, in order to transition to commercially available LCIG.

Reporting group title	Extension/Transition OMT->LCIG

Reporting group description:

Participants randomized to continue OMT in the United States or South Korea who elected to enter an Extension/Transition follow-up period to receive an individually optimized LCIG dose (after NJ and/or PEG-J placement), in order to transition to commercially available LCIG.

Reporting group title	LCIG

Reporting group description:

Participants randomized to LCIG at an individually optimized dose, in accordance with the LCIG approved product label for countries participating in the study during the 26-week treatment phase. Changes to anti-PD and NMS medications were to remain stable and were only made if medically indicated.

The total daily dose of LCIG was composed of 3 components: (i) the morning dose, (ii) continuous maintenance infusion dose and (iii) extra doses. The continuous infusion was expected to run over a period of 16 consecutive hours each day.

Serious adverse events	Optimized Medical Treatment (OMT)	Extension/Transition LCIG ->LCIG	Extension/Transition OMT->LCIG
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 44 (9.09%)	1 / 14 (7.14%)	2 / 10 (20.00%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events	0	0	1
Injury, poisoning and procedural complications			
FALL			

subjects affected / exposed	0 / 44 (0.00%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PATELLA FRACTURE			
subjects affected / exposed	0 / 44 (0.00%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LOWER LIMB FRACTURE			
subjects affected / exposed	0 / 44 (0.00%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HUMERUS FRACTURE			
subjects affected / exposed	0 / 44 (0.00%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FEMUR FRACTURE			
subjects affected / exposed	1 / 44 (2.27%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUBDURAL HAEMATOMA			
subjects affected / exposed	0 / 44 (0.00%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
AORTIC VALVE STENOSIS			
subjects affected / exposed	0 / 44 (0.00%)	0 / 14 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
NEURALGIA			
subjects affected / exposed	0 / 44 (0.00%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SYNCOPE			

subjects affected / exposed	0 / 44 (0.00%)	0 / 14 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PARKINSON'S DISEASE			
subjects affected / exposed	1 / 44 (2.27%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	0 / 44 (0.00%)	0 / 14 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DEATH			
subjects affected / exposed	0 / 44 (0.00%)	0 / 14 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Gastrointestinal disorders			
PNEUMOPERITONEUM			
subjects affected / exposed	0 / 44 (0.00%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INGUINAL HERNIA			
subjects affected / exposed	0 / 44 (0.00%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ILEUS PARALYTIC			
subjects affected / exposed	0 / 44 (0.00%)	0 / 14 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
PNEUMONIA ASPIRATION			

subjects affected / exposed	0 / 44 (0.00%)	0 / 14 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DYSPNOEA			
subjects affected / exposed	0 / 44 (0.00%)	0 / 14 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
DEPRESSION			
subjects affected / exposed	0 / 44 (0.00%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
ROTATOR CUFF SYNDROME			
subjects affected / exposed	0 / 44 (0.00%)	1 / 14 (7.14%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
BACTERAEMIA			
subjects affected / exposed	1 / 44 (2.27%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERITONITIS			
subjects affected / exposed	0 / 44 (0.00%)	0 / 14 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URINARY TRACT INFECTION			
subjects affected / exposed	1 / 44 (2.27%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
STOMA SITE INFECTION			
subjects affected / exposed	0 / 44 (0.00%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

PYELONEPHRITIS ACUTE			
subjects affected / exposed	0 / 44 (0.00%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA			
subjects affected / exposed	0 / 44 (0.00%)	0 / 14 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Metabolism and nutrition disorders			
KETOACIDOSIS			
subjects affected / exposed	0 / 44 (0.00%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	LCIG		
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 43 (20.93%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
FALL			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
PATELLA FRACTURE			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
LOWER LIMB FRACTURE			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
HUMERUS FRACTURE			

subjects affected / exposed	1 / 43 (2.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
FEMUR FRACTURE				
subjects affected / exposed	1 / 43 (2.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
SUBDURAL HAEMATOMA				
subjects affected / exposed	1 / 43 (2.33%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
AORTIC VALVE STENOSIS				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
NEURALGIA				
subjects affected / exposed	1 / 43 (2.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
SYNCOPE				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
PARKINSON'S DISEASE				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
ASTHENIA				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

DEATH			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
PNEUMOPERITONEUM			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
INGUINAL HERNIA			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
ILEUS PARALYTIC			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
PNEUMONIA ASPIRATION			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
DYSPNOEA			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
DEPRESSION			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
ROTATOR CUFF SYNDROME			

subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
BACTERAEMIA			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
PERITONITIS			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
URINARY TRACT INFECTION			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
STOMA SITE INFECTION			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
PYELONEPHRITIS ACUTE			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
PNEUMONIA			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
KETOACIDOSIS			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Optimized Medical Treatment (OMT)	Extension/Transition LCIG ->LCIG	Extension/Transition OMT->LCIG
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 44 (29.55%)	4 / 14 (28.57%)	6 / 10 (60.00%)
Investigations			
WEIGHT DECREASED			
subjects affected / exposed	0 / 44 (0.00%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
VITAMIN B6 DECREASED			
subjects affected / exposed	1 / 44 (2.27%)	1 / 14 (7.14%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Injury, poisoning and procedural complications			
STOMA SITE DERMATITIS			
subjects affected / exposed	0 / 44 (0.00%)	0 / 14 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
PROCEDURAL PAIN			
subjects affected / exposed	0 / 44 (0.00%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
FALL			
subjects affected / exposed	7 / 44 (15.91%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	8	0	0
STOMA SITE DISCHARGE			
subjects affected / exposed	0 / 44 (0.00%)	0 / 14 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
STOMA SITE PAIN			
subjects affected / exposed	0 / 44 (0.00%)	1 / 14 (7.14%)	3 / 10 (30.00%)
occurrences (all)	0	1	6
STOMA SITE HYPERGRANULATION			
subjects affected / exposed	0 / 44 (0.00%)	0 / 14 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
Nervous system disorders			
PERIPHERAL SENSORY NEUROPATHY			
subjects affected / exposed	0 / 44 (0.00%)	0 / 14 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
PARKINSON'S DISEASE			

subjects affected / exposed	3 / 44 (6.82%)	1 / 14 (7.14%)	0 / 10 (0.00%)
occurrences (all)	3	1	0
FREEZING PHENOMENON			
subjects affected / exposed	3 / 44 (6.82%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	4	0	0
DYSKINESIA			
subjects affected / exposed	1 / 44 (2.27%)	0 / 14 (0.00%)	2 / 10 (20.00%)
occurrences (all)	1	0	2
General disorders and administration site conditions			
PYREXIA			
subjects affected / exposed	0 / 44 (0.00%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
CHEST PAIN			
subjects affected / exposed	0 / 44 (0.00%)	0 / 14 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Eye disorders			
CATARACT NUCLEAR			
subjects affected / exposed	0 / 44 (0.00%)	1 / 14 (7.14%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
NORMAL TENSION GLAUCOMA			
subjects affected / exposed	0 / 44 (0.00%)	1 / 14 (7.14%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Social circumstances			
SOCIAL PROBLEM			
subjects affected / exposed	0 / 44 (0.00%)	0 / 14 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
ABDOMINAL DISTENSION			
subjects affected / exposed	0 / 44 (0.00%)	0 / 14 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
ABDOMINAL DISCOMFORT			
subjects affected / exposed	0 / 44 (0.00%)	0 / 14 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
DIARRHOEA			
subjects affected / exposed	1 / 44 (2.27%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0

DUODENAL ULCER			
subjects affected / exposed	0 / 44 (0.00%)	0 / 14 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
DYSPEPSIA			
subjects affected / exposed	0 / 44 (0.00%)	0 / 14 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
DYSPHAGIA			
subjects affected / exposed	0 / 44 (0.00%)	0 / 14 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
GASTRIC MUCOSAL LESION			
subjects affected / exposed	0 / 44 (0.00%)	0 / 14 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
GASTRIC ULCER			
subjects affected / exposed	0 / 44 (0.00%)	0 / 14 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
GASTROOESOPHAGEAL REFLUX DISEASE			
subjects affected / exposed	0 / 44 (0.00%)	0 / 14 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
CONSTIPATION			
subjects affected / exposed	0 / 44 (0.00%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
ABDOMINAL PAIN			
subjects affected / exposed	0 / 44 (0.00%)	1 / 14 (7.14%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Respiratory, thoracic and mediastinal disorders			
PRODUCTIVE COUGH			
subjects affected / exposed	1 / 44 (2.27%)	0 / 14 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
COUGH			
subjects affected / exposed	1 / 44 (2.27%)	0 / 14 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
HYPOXIA			
subjects affected / exposed	0 / 44 (0.00%)	0 / 14 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Psychiatric disorders			

AGITATION			
subjects affected / exposed	0 / 44 (0.00%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
ANXIETY			
subjects affected / exposed	0 / 44 (0.00%)	0 / 14 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
DEPRESSED MOOD			
subjects affected / exposed	0 / 44 (0.00%)	0 / 14 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
DEPRESSION			
subjects affected / exposed	0 / 44 (0.00%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
HALLUCINATION			
subjects affected / exposed	0 / 44 (0.00%)	0 / 14 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
SLEEP ATTACKS			
subjects affected / exposed	0 / 44 (0.00%)	1 / 14 (7.14%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
PSYCHOTIC DISORDER			
subjects affected / exposed	0 / 44 (0.00%)	0 / 14 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
INSOMNIA			
subjects affected / exposed	0 / 44 (0.00%)	1 / 14 (7.14%)	1 / 10 (10.00%)
occurrences (all)	0	1	2
IMPULSIVE BEHAVIOUR			
subjects affected / exposed	0 / 44 (0.00%)	1 / 14 (7.14%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
IMPULSE-CONTROL DISORDER			
subjects affected / exposed	0 / 44 (0.00%)	0 / 14 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Infections and infestations			
STOMA SITE INFECTION			
subjects affected / exposed	0 / 44 (0.00%)	0 / 14 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
STOMA SITE CELLULITIS			

subjects affected / exposed	0 / 44 (0.00%)	0 / 14 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
ASYMPTOMATIC COVID-19			
subjects affected / exposed	0 / 44 (0.00%)	0 / 14 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1

Non-serious adverse events	LCIG		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 43 (76.74%)		
Investigations			
WEIGHT DECREASED			
subjects affected / exposed	4 / 43 (9.30%)		
occurrences (all)	4		
VITAMIN B6 DECREASED			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences (all)	2		
Injury, poisoning and procedural complications			
STOMA SITE DERMATITIS			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
PROCEDURAL PAIN			
subjects affected / exposed	4 / 43 (9.30%)		
occurrences (all)	4		
FALL			
subjects affected / exposed	4 / 43 (9.30%)		
occurrences (all)	6		
STOMA SITE DISCHARGE			
subjects affected / exposed	4 / 43 (9.30%)		
occurrences (all)	4		
STOMA SITE PAIN			
subjects affected / exposed	6 / 43 (13.95%)		
occurrences (all)	7		
STOMA SITE HYPERGRANULATION			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	3		
Nervous system disorders			

PERIPHERAL SENSORY NEUROPATHY subjects affected / exposed occurrences (all) PARKINSON'S DISEASE subjects affected / exposed occurrences (all) FREEZING PHENOMENON subjects affected / exposed occurrences (all) DYSKINESIA subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0 2 / 43 (4.65%) 3 1 / 43 (2.33%) 2 4 / 43 (9.30%) 4		
General disorders and administration site conditions PYREXIA subjects affected / exposed occurrences (all) CHEST PAIN subjects affected / exposed occurrences (all)	4 / 43 (9.30%) 4 0 / 43 (0.00%) 0		
Eye disorders CATARACT NUCLEAR subjects affected / exposed occurrences (all) NORMAL TENSION GLAUCOMA subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0 0 / 43 (0.00%) 0		
Social circumstances SOCIAL PROBLEM subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0		
Gastrointestinal disorders ABDOMINAL DISTENSION subjects affected / exposed occurrences (all) ABDOMINAL DISCOMFORT	2 / 43 (4.65%) 2		

subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
DIARRHOEA			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	3		
DUODENAL ULCER			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
DYSPEPSIA			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
DYSPHAGIA			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
GASTRIC MUCOSAL LESION			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
GASTRIC ULCER			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
GASTROOESOPHAGEAL REFLUX DISEASE			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
CONSTIPATION			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	3		
ABDOMINAL PAIN			
subjects affected / exposed	5 / 43 (11.63%)		
occurrences (all)	6		
Respiratory, thoracic and mediastinal disorders			
PRODUCTIVE COUGH			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
COUGH			

subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
HYPOXIA			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Psychiatric disorders			
AGITATION			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	3		
ANXIETY			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences (all)	2		
DEPRESSED MOOD			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
DEPRESSION			
subjects affected / exposed	4 / 43 (9.30%)		
occurrences (all)	4		
HALLUCINATION			
subjects affected / exposed	4 / 43 (9.30%)		
occurrences (all)	4		
SLEEP ATTACKS			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
PSYCHOTIC DISORDER			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
INSOMNIA			
subjects affected / exposed	4 / 43 (9.30%)		
occurrences (all)	4		
IMPULSIVE BEHAVIOUR			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
IMPULSE-CONTROL DISORDER			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		

Infections and infestations			
STOMA SITE INFECTION			
subjects affected / exposed	5 / 43 (11.63%)		
occurrences (all)	5		
STOMA SITE CELLULITIS			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
ASYMPTOMATIC COVID-19			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 May 2015	• Clarify that the study will be performed in compliance with ICH-GCP E6(R1). • Add screening for alcohol abuse. • Clarify that a movement disorder specialist should perform the interview at screening. • Clarify that all subjects, selected for the study will be judged to have decision-making capacity, or will have a caregiver, who has the legal right to act on behalf of the subject following national laws. • To remove the double-barrier method as an acceptable birth control option. • To allow the Investigator to adjust the anti-PD medications without consulting the Medical Monitor. • To remove the Bazett's correction method (QTcB) from the ECG analysis. • To include the text regarding experience for blinded raters. • To state that protocol deviations affecting subject safety or data robustness should be reported in EU Member States where this is required.
28 March 2016	• Incorporate Administrative Change 1. • Update PC (Product Complaints) Section. • Clarify the first treatment day for the OMT group. • Birth Control Inclusion/Exclusion section of the protocol. • To clarify that all tests at V1 will be used to determine inclusion/exclusion criteria. • To update Table 3, Study Activities. • To clarify how data are collected by the blinded raters.
15 November 2016	• Increase the number of sites participating in the study. • Relax the inclusion criteria by lowering the score of the PDSS-2 assessment administrated at baseline from 20 to 18. • Remove Exclusion Criterion 3: Subject has undergone apomorphine continuous infusion for the treatment of Parkinson's disease. • Remove Drug/Alcohol Screening from Visit 3. • Update the Contraception Recommendations and Pregnancy Testing guidelines, including monthly pregnancy testing for women of child bearing potential (WOCBP). • Update definitions of Relationship to Study Drug.
31 May 2017	• Change the study Reference Safety Information (RSI) from the Duodopa Summary of Product Characteristics (SmPC) to the Levodopa-Carbidopa Intestinal Gel (LCIG), (also known as Duopa or Duodopa) Investigator Brochure (IB).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported