Clinical trial results:
An Open-label, Randomized 12 Week Study Comparing Efficacy of Levodopa-Carbidopa Intestinal Gel/Carbidopa-Levodopa Enteral Suspension and Optimized Medical Treatment on Dyskinesia in Subjects with Advanced Parkinson's Disease

Summary

EudraCT number	2016-001403-23
Trial protocol	FI SK GR ES HU IT
Global end of trial date	19 September 2019

Results information

Result version number	v1 (current)
This version publication date	03 September 2020
First version publication date	03 September 2020

Trial information

Trial identification

Sponsor protocol code	M15-535

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02799381
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AbbVie
Sponsor organisation address	AbbVie House, Vanwall Business Park, Vanwall Road, Maidenhead, Berkshire, United Kingdom, SL6-4UB
Public contact	AbbVie, Global Medical Services, 001 8006339110, abbvieclinicaltrials@abbvie.com
Scientific contact	AbbVie, Global Medical Services, 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	19 September 2019
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	19 September 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this Phase 3b, open-label, randomized, multicenter, 12-week study was to examine the effect of levodopa-carbidopa intestinal gel (LCIG) compared with optimized medical treatment (OMT) on dyskinesia in participants with advanced Parkinson's disease (PD). The study consisted of 3 sequential periods: Screening, Treatment, and Follow-Up. The OMT group had the same schedule of visits/procedures throughout the study as the LCIG treatment group, except for visits related to nasojejunal (NJ)/percutaneous endoscopic gastrostomy (PEG) procedures, titration of LCIG, and follow-up period.

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	09 February 2017
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	Slovakia: 12
Country: Number of subjects enrolled	Spain: 18
Country: Number of subjects enrolled	United States: 1
Country: Number of subjects enrolled	Finland: 6
Country: Number of subjects enrolled	Greece: 7
Country: Number of subjects enrolled	Hungary: 6
Country: Number of subjects enrolled	Italy: 13
Worldwide total number of subjects	63
EEA total number of subjects	62

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)	10
From 65 to 84 years	53
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Safety Data Set: all participants randomized to OMT and all participants randomized to LCIG treatment who had a study tube (NJ or PEG-J) placement procedure. Two participants randomized to the LCIG arm did not have device placement for LCIG infusion and were not included in the safety data set.

Period 1

Period 1 title	Overall Study (overall 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 (OMT)

Arm description:

Participants randomized to OMT continued their current anti Parkinson’s disease (anti-PD) medication regimen for the duration of the study. All anti-PD medications and medications to treat dyskinesia must have remained stable for the duration of the study unless adjustments were medically indicated. The Investigator provided the prescription for continued OMT.

Arm type	Active comparator
Investigational medicinal product name	Optimized antiparkinsonian treatment
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Tablet, Transdermal patch
Routes of administration	Oral use, Transdermal use

Dosage and administration details:

Dose levels of prescribed antiparkinsonian medications were individually optimized to their maximum therapeutic effect.

Arm title	Levodopa-Carbidopa Intestinal Gel (LCIG)

Arm description:

The total daily dose of infusion LCIG was composed of three components: (i) the morning dose, (ii) continuous maintenance infusion dose and (iii) extra doses. A temporary nasojejunal (NJ) tube may have been used initially with the infusion pump to determine a participant’s response to this method of treatment and to optimize the dose of LCIG before treatment with a permanent percutaneous endoscopic gastrostomy - with jejunal extension (PEG-J) tube was started. Following optional NJ and/or PEG-J placement and, at the investigator's discretion, the participant may have begun initiation and titration of LCIG infusion on Day 1 once tube placement was confirmed. The dose of LCIG was adjusted to obtain the optimal clinical response. The rate of LCIG infusion is typically within the range of 1 to 10 mL/hour (20 to 200 mg of levodopa/hour) in most instances and runs over a period of 16 consecutive hours each day.

Arm type	Experimental
Investigational medicinal product name	Levodopa-Carbidopa Intestinal Gel (LCIG)
Investigational medicinal product code	
Other name	ABT-SLV187, DUOPA (carbidopa and levodopa Enteral Suspension), DUODOPA
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intestinal use

Dosage and administration details:

Dose levels were individually optimized.

Number of subjects in period 1[1]	Optimized Medical Treatment (OMT)	Levodopa-Carbidopa Intestinal Gel (LCIG)
Started	33	28
Completed	29	25
Not completed	4	3
Participant did not take any study drug	1	-
Adverse event, non-fatal	-	1
Withdrew consent	3	2

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Two participants randomized to the LCIG arm did not have device placement for LCIG infusion and were not included in the safety data set.

Baseline characteristics

Reporting groups	
Reporting group title	Optimized Medical Treatment (OMT)

Reporting group description:

Participants randomized to OMT continued their current anti Parkinson's disease (anti-PD) medication regimen for the duration of the study. All anti-PD medications and medications to treat dyskinesia must have remained stable for the duration of the study unless adjustments were medically indicated. The Investigator provided the prescription for continued OMT.

Reporting group title	Levodopa-Carbidopa Intestinal Gel (LCIG)

Reporting group description:

The total daily dose of infusion LCIG was composed of three components: (i) the morning dose, (ii) continuous maintenance infusion dose and (iii) extra doses. A temporary nasojejunal (NJ) tube may have been used initially with the infusion pump to determine a participant's response to this method of treatment and to optimize the dose of LCIG before treatment with a permanent percutaneous endoscopic gastrostomy - with jejunal extension (PEG-J) tube was started. Following optional NJ and/or PEG-J placement and, at the investigator's discretion, the participant may have begun initiation and titration of LCIG infusion on Day 1 once tube placement was confirmed. The dose of LCIG was adjusted to obtain the optimal clinical response. The rate of LCIG infusion is typically within the range of 1 to 10 mL/hour (20 to 200 mg of levodopa/hour) in most instances and runs over a period of 16 consecutive hours each day.

Reporting group values	Optimized Medical Treatment (OMT)	Levodopa-Carbidopa Intestinal Gel (LCIG)	Total
Number of subjects	33	28	61
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	68.7	69.3	
standard deviation	± 7.20	± 6.99	-
Gender categorical Units: Subjects			
Female	16	16	32
Male	17	12	29

End points

End points reporting groups

Reporting group title	Optimized Medical Treatment (OMT)

Reporting group description:

Participants randomized to OMT continued their current anti Parkinson's disease (anti-PD) medication regimen for the duration of the study. All anti-PD medications and medications to treat dyskinesia must have remained stable for the duration of the study unless adjustments were medically indicated. The Investigator provided the prescription for continued OMT.

Reporting group title	Levodopa-Carbidopa Intestinal Gel (LCIG)

Reporting group description:

The total daily dose of infusion LCIG was composed of three components: (i) the morning dose, (ii) continuous maintenance infusion dose and (iii) extra doses. A temporary nasojejunal (NJ) tube may have been used initially with the infusion pump to determine a participant's response to this method of treatment and to optimize the dose of LCIG before treatment with a permanent percutaneous endoscopic gastrostomy - with jejunal extension (PEG-J) tube was started. Following optional NJ and/or PEG-J placement and, at the investigator's discretion, the participant may have begun initiation and titration of LCIG infusion on Day 1 once tube placement was confirmed. The dose of LCIG was adjusted to obtain the optimal clinical response. The rate of LCIG infusion is typically within the range of 1 to 10 mL/hour (20 to 200 mg of levodopa/hour) in most instances and runs over a period of 16 consecutive hours each day.

Primary: Mean Change from Baseline to Week 12 in Unified Dyskinesia Rating Scale (UDysRS) Total Score

End point title	Mean Change from Baseline to Week 12 in Unified Dyskinesia Rating Scale (UDysRS) Total Score

End point description:

The Unified Dyskinesia Rating Scale (UDysRS) is a tool used to assess dyskinesia in Parkinson's disease (PD) and contains both self-evaluation questions and items that are assessed directly by the physician to objectively rate the abnormal movements associated with PD. Part 1 contains 11 questions about the ON time dyskinesia and the impact of ON-dyskinesia on experiences of daily living. Part 2 contains 4 questions about OFF-dystonia rating. Part 3 contains 7 questions about objective evaluation of dyskinesia impairment and Part 4 contains 4 questions regarding dyskinesia disability. Each question is scored with respect to severity, which is rated on a scale where 0 = normal, 1 = slight, 2 = mild, 3= moderate and 4 = severe. The UDysRS total score is obtained by summing the item scores, ranging from 0 to 104. Higher scores are associated with more disability. Negative changes from baseline indicate improvement.

End point type	Primary

End point timeframe:

Baseline, Week 12

End point values	Optimized Medical Treatment (OMT)	Levodopa-Carbidopa Intestinal Gel (LCIG)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26[1]	24[2]		
Units: units on a scale				
least squares mean (standard error)	-2.33 (± 2.56)	-17.37 (± 2.79)		

Notes:

[1] - Intent-to-treat (ITT): subjects with available data at Wk 12 who were randomized to the OMT group

[2] - ITT: randomized w/available data at Wk 12 who rcvd ≥ 1 dose of study drug after PEG-J placement

Statistical analyses

Statistical analysis title	Change from baseline to Week 12

Statistical analysis description:

The likelihood-based mixed-effects model repeated measures (MMRM) analysis of the change from baseline to Week 12 used all observed data. The model included fixed, categorical effects for treatment, country, visit, and treatment-by-visit interaction, with continuous fixed covariates for baseline score and the baseline score-by-visit interaction.

Comparison groups	Optimized Medical Treatment (OMT) v Levodopa-Carbidopa Intestinal Gel (LCIG)
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	Mixed-effects model repeated measures
Parameter estimate	LS Mean Difference (LCIG-OMT) at Week 12
Point estimate	-15.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.47
upper limit	-8.63

Notes:

[3] - Two-sided p-value

Secondary: Mean Change from Baseline to Week 12 in ON time without troublesome dyskinesia

End point title	Mean Change from Baseline to Week 12 in ON time without troublesome dyskinesia

End point description:

The Parkinson's Disease (PD) Symptom Diary is completed every 30 minutes for the full 24 hours of each of 3 days prior to selected study visits. It reflects both time awake and time asleep. Daily totals are normalized to a 16-hour scale (i.e., 16 hours of awake time). The normalized totals for the 3 days prior to the visit are averaged for the analysis. ON time is when PD symptoms are well controlled by the drug, and OFF time is when PD symptoms are not adequately controlled by the drug. Positive change from baseline for ON time without troublesome dyskinesia indicates improvement.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Optimized Medical Treatment (OMT)	Levodopa-Carbidopa Intestinal Gel (LCIG)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28[4]	25[5]		
Units: hours				
least squares mean (standard error)	-0.12 (± 0.63)	3.15 (± 0.69)		

Notes:

[4] - Intent-to-treat (ITT): subjects with available data at Wk 12 who were randomized to the OMT group

[5] - ITT: randomized w/available data at Wk 12 who rcvd ≥ 1 dose of study drug after PEG-J placement

Statistical analyses

Statistical analysis title	Change from baseline to Week 12

Statistical analysis description:

If the primary efficacy variable was statistically significant, each of the secondary variables were to be tested using a fixed sequence as a gatekeeping procedure and at α level of 0.050. Testing was to cease at the point that a secondary variable failed to demonstrate statistical significance.

Comparison groups	Optimized Medical Treatment (OMT) v Levodopa-Carbidopa Intestinal Gel (LCIG)
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	< 0.0001 [7]
Method	Mixed-effects model repeated measures
Parameter estimate	LS Mean Difference (LCIG-OMT) at Week 12
Point estimate	3.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.71
upper limit	4.83

Notes:

[6] - The likelihood-based mixed-effects model repeated measures (MMRM) analysis of the change from baseline to Week 12 used all observed data. The model included fixed, categorical effects for treatment, country, visit, and treatment-by-visit interaction, with continuous fixed covariates for baseline score and the baseline score-by-visit interaction.

[7] - Two-sided p-value

Secondary: Mean Change from Baseline to Week 12 in Parkinson's Disease Questionnaire-8 (PDQ-8) Summary Index

End point title	Mean Change from Baseline to Week 12 in Parkinson's Disease Questionnaire-8 (PDQ-8) Summary Index

End point description:

The Parkinson's Disease Questionnaire-8 (PDQ-8) is a disease-specific instrument designed to measure aspects of health that are relevant to participants with PD, and which may not be included in general health status questionnaires. The PDQ-8 is a self-administered questionnaire. Each item is scored on the following 5-point scale: 0 = Never, 1 = Occasionally, 2 = Sometimes, 3 = Often, 4 = Always (or cannot do at all, if applicable). Higher scores are consistently associated with the more severe symptoms of the disease such as tremors and stiffness. The results are presented as a summary index. The PDQ-8 summary index ranges from 0 to 100, where lower scores indicate a better perceived health status. Negative changes from baseline indicate improvement.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Optimized Medical Treatment (OMT)	Levodopa-Carbidopa Intestinal Gel (LCIG)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29[8]	25[9]		
Units: units on a scale				
least squares mean (standard error)	-4.95 (± 3.11)	-21.62 (± 3.47)		

Notes:

[8] - Intent-to-treat (ITT): subjects with available data at Wk 12 who were randomized to the OMT group

[9] - ITT: randomized w/available data at Wk 12 who rcvd ≥ 1 dose of study drug after PEG-J placement

Statistical analyses

Statistical analysis title	Change from baseline to Week 12

Statistical analysis description:

If the primary efficacy variable was statistically significant, each of the secondary variables were to be tested using a fixed sequence as a gatekeeping procedure and at α level of 0.050. Testing was to cease at the point that a secondary variable failed to demonstrate statistical significance.

Comparison groups	Optimized Medical Treatment (OMT) v Levodopa-Carbidopa Intestinal Gel (LCIG)
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	< 0.0001 [11]
Method	Mixed-effects model repeated measures
Parameter estimate	LS Mean Difference (LCIG-OMT) at Week 12
Point estimate	-16.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.48
upper limit	-8.85

Notes:

[10] - The likelihood-based mixed-effects model repeated measures (MMRM) analysis of the change from baseline to Week 12 used all observed data. The model included fixed, categorical effects for treatment, country, visit, and treatment-by-visit interaction, with continuous fixed covariates for baseline score and the baseline score-by-visit interaction.

[11] - Two-sided p-value

Secondary: Mean Clinical Global Impression of Change (CGI-C) Score at Week 12

End point title	Mean Clinical Global Impression of Change (CGI-C) Score at Week 12

End point description:

The Clinical Global Impression of Change (CGI-C) score is a clinician's rating scale for assessing Global Improvement of Change. The CGI-C rates improvement by 7 categories: very much improved (1), much improved (2), minimally improved (3), no change (4), minimally worse (5), much worse (6), very much worse (7). The CGI-C score ranges from 1 to 7, with lower scores indicating improvement.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Optimized Medical Treatment (OMT)	Levodopa-Carbidopa Intestinal Gel (LCIG)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29[12]	25[13]		
Units: units on a scale				
least squares mean (standard error)	4.58 (± 0.25)	2.48 (± 0.28)		

Notes:

[12] - Intent-to-treat (ITT): subjects with available data at Wk 12 who were randomized to the OMT group

[13] - ITT: randomized w/available data at Wk 12 who rcvd ≥ 1 dose of study drug after PEG-J placement

Statistical analyses

Statistical analysis title	CGI-C Score at Week 12

Statistical analysis description:

If the primary efficacy variable was statistically significant, each of the secondary variables were to be tested using a fixed sequence as a gatekeeping procedure and at α level of 0.050. Testing was to cease at the point that a secondary variable failed to demonstrate statistical significance.

Comparison groups	Optimized Medical Treatment (OMT) v Levodopa-Carbidopa Intestinal Gel (LCIG)
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority[14]
P-value	< 0.0001 [15]
Method	Mixed-effects model repeated measures
Parameter estimate	LS Mean Difference (LCIG-OMT) at Week 12
Point estimate	-2.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.78
upper limit	-1.44

Notes:

[14] - The likelihood-based mixed-effects model repeated measures (MMRM) analysis of the change from baseline to Week 12 used all observed data. The model included fixed, categorical effects for treatment, country, visit, and treatment-by-visit interaction, with continuous fixed covariates for baseline score and the baseline score-by-visit interaction.

[15] - Two-sided p-value

Secondary: Mean Change From Baseline to Week 12 in Unified Parkinson's Disease Rating Scale (UPDRS) Part II Score (Activities of Daily Living)

End point title	Mean Change From Baseline to Week 12 in Unified Parkinson's Disease Rating Scale (UPDRS) Part II Score (Activities of Daily Living)

End point description:

The Unified Parkinson's Disease Rating Scale (UPDRS) is an Investigator-used rating tool to follow the longitudinal course of Parkinson's disease. The Part II score is the sum of the answers to the 13 questions related to Activities of Daily Living, and ranges from 0-52. Higher scores are associated with more disability. Negative values indicate improvement from baseline.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Optimized Medical Treatment (OMT)	Levodopa-Carbidopa Intestinal Gel (LCIG)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29[16]	24[17]		
Units: units on a scale				
least squares mean (standard error)	0.21 (± 1.16)	-5.33 (± 1.28)		

Notes:

[16] - Intent-to-treat (ITT): subjects with available data at Wk 12 who were randomized to the OMT group
[17] - ITT: randomized w/available data at Wk 12 who rcvd ≥ 1 dose of study drug after PEG-J placement

Statistical analyses

Statistical analysis title	Change from baseline to Week 12

Statistical analysis description:

If the primary efficacy variable was statistically significant, each of the secondary variables were to be tested using a fixed sequence as a gatekeeping procedure and at α level of 0.050. Testing was to cease at the point that a secondary variable failed to demonstrate statistical significance.

Comparison groups	Optimized Medical Treatment (OMT) v Levodopa-Carbidopa Intestinal Gel (LCIG)
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority[18]
P-value	= 0.0006 [19]
Method	Mixed-effects model repeated measures
Parameter estimate	LS Mean Difference (LCIG-OMT) at Week 12
Point estimate	-5.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.59
upper limit	-2.49

Notes:

[18] - The likelihood-based mixed-effects model repeated measures (MMRM) analysis of the change from baseline to Week 12 used all observed data. The model included fixed, categorical effects for treatment, country, visit, and treatment-by-visit interaction, with continuous fixed covariates for baseline score and the baseline score-by-visit interaction.

[19] - Two-sided p-value

Secondary: Mean Change from Baseline to Week 12 in Unified Parkinson's Disease Rating Scale (UPDRS) Part III Score (Motor Examination)

End point title	Mean Change from Baseline to Week 12 in Unified Parkinson's

	Disease Rating Scale (UPDRS) Part III Score (Motor Examination)

End point description:

The Unified Parkinson's Disease Rating Scale (UPDRS) is an Investigator-used rating tool to follow the longitudinal course of Parkinson's disease. The Part III score is the sum of the 27 answers related to Motor Examination, and ranges from 0-108. Higher scores are associated with more disability. Negative values indicate improvement from baseline.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Optimized Medical Treatment (OMT)	Levodopa-Carbidopa Intestinal Gel (LCIG)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29[20]	25[21]		
Units: units on a scale				
least squares mean (standard error)	-0.87 (± 1.89)	-4.93 (± 2.08)		

Notes:

[20] - Intent-to-treat (ITT): subjects with available data at Wk 12 who were randomized to the OMT group
[21] - ITT: randomized w/available data at Wk 12 who rcvd ≥ 1 dose of study drug after PEG-J placement

Statistical analyses

Statistical analysis title	Change from baseline to Week 12

Statistical analysis description:

If the primary efficacy variable was statistically significant, each of the secondary variables were to be tested using a fixed sequence as a gatekeeping procedure and at α level of 0.050. Testing was to cease at the point that a secondary variable failed to demonstrate statistical significance.

Comparison groups	Optimized Medical Treatment (OMT) v Levodopa-Carbidopa Intestinal Gel (LCIG)
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority[22]
P-value	= 0.0762 [23]
Method	Mixed-effects model repeated measures
Parameter estimate	LS Mean Difference (LCIG-OMT) at Week 12
Point estimate	-4.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.55
upper limit	0.44

Notes:

[22] - The likelihood-based mixed-effects model repeated measures (MMRM) analysis of the change from baseline to Week 12 used all observed data. The model included fixed, categorical effects for treatment, country, visit, and treatment-by-visit interaction, with continuous fixed covariates for baseline score and the baseline score-by-visit interaction.

[23] - Two-sided p-value

Secondary: Mean Change from Baseline to Week 12 in OFF time

End point title	Mean Change from Baseline to Week 12 in OFF time

End point description:

The Parkinson's Disease (PD) Symptom Diary is completed every 30 minutes for the full 24 hours of each of 3 days prior to selected study visits. It reflects both time awake and time asleep. Daily totals are normalized to a 16-hour scale (i.e., 16 hours of awake time). The normalized totals for the 3 days prior to the visit are averaged for the analysis. ON time is when PD symptoms are well controlled by the drug, and OFF time is when PD symptoms are not adequately controlled by the drug. Negative change from baseline for OFF time indicates improvement.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Optimized Medical Treatment (OMT)	Levodopa-Carbidopa Intestinal Gel (LCIG)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28[24]	25[25]		
Units: hours				
least squares mean (standard error)	0.18 (± 0.49)	-2.17 (± 0.53)		

Notes:

[24] - Intent-to-treat (ITT): subjects with available data at Wk 12 who were randomized to the OMT group
[25] - ITT: randomized w/available data at Wk 12 who rcvd ≥ 1 dose of study drug after PEG-J placement

Statistical analyses

Statistical analysis title	Change from baseline to Week 12

Statistical analysis description:

If the primary efficacy variable was statistically significant, each of the secondary variables were to be tested using a fixed sequence as a gatekeeping procedure and at α level of 0.050. Testing was to cease at the point that a secondary variable failed to demonstrate statistical significance.

Comparison groups	Optimized Medical Treatment (OMT) v Levodopa-Carbidopa Intestinal Gel (LCIG)
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority[26]
P-value	= 0.0002 [27]
Method	Mixed-effects model repeated measures
Parameter estimate	LS Mean Difference (LCIG-OMT) at Week 12
Point estimate	-2.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.51
upper limit	-1.19

Notes:

[26] - The likelihood-based mixed-effects model repeated measures (MMRM) analysis of the change from baseline to Week 12 used all observed data. The model included fixed, categorical effects for treatment, country, visit, and treatment-by-visit interaction, with continuous fixed covariates for baseline score and the baseline score-by-visit interaction.

[27] - Two-sided p-value

Adverse events

Adverse events information

Timeframe for reporting adverse events:

TEAEs /TESAEs: OMT after randomization until 30 d after last visit, ≤ 18 wks; LCIG study tubes removed after last Tx, from tube placement up to 30 d after tube removal, ≤ 16 wks; other LCIG: from tube placement up to 30 d after last study visit, ≤ 16 wks

Adverse event reporting additional description:

TEAEs and SAEs are defined as any adverse event (AE) with onset date after the day of randomization (OMT group) or from time of tube placement (LCIG group) until 30 d after the last visit (OMT group), or up to 30 d following tube removal (LCIG group) or the last study visit (LCIG group) and were collected whether elicited or spontaneously reported.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Levodopa-Carbidopa Intestinal Gel (LCIG)

Reporting group description:

The total daily dose of infusion LCIG was composed of three components: (i) the morning dose, (ii) continuous maintenance infusion dose and (iii) extra doses. A temporary nasojejunal (NJ) tube may have been used initially with the infusion pump to determine a participant's response to this method of treatment and to optimize the dose of LCIG before treatment with a permanent percutaneous endoscopic gastrostomy - with jejunal extension (PEG-J) tube was started. Following optional NJ and/or PEG-J placement and, at the investigator's discretion, the participant may have begun initiation and titration of LCIG infusion on Day 1 once tube placement was confirmed. The dose of LCIG was adjusted to obtain the optimal clinical response. The rate of LCIG infusion is typically within the range of 1 to 10 mL/hour (20 to 200 mg of levodopa/hour) in most instances and runs over a period of 16 consecutive hours each day.

Reporting group title	Optimized Medical Treatment (OMT)

Reporting group description:

Participants randomized to OMT continued their current anti Parkinson's disease (anti-PD) medication regimen for the duration of the study. All anti-PD medications and medications to treat dyskinesia must have remained stable for the duration of the study unless adjustments were medically indicated. The Investigator provided the prescription for continued OMT.

Serious adverse events	Levodopa-Carbidopa Intestinal Gel (LCIG)	Optimized Medical Treatment (OMT)	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 28 (7.14%)	0 / 33 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	1 / 28 (3.57%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

SYNCOPE			
subjects affected / exposed	1 / 28 (3.57%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
PNEUMOPERITONEUM			
subjects affected / exposed	1 / 28 (3.57%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
CYSTITIS			
subjects affected / exposed	1 / 28 (3.57%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Levodopa-Carbidopa Intestinal Gel (LCIG)	Optimized Medical Treatment (OMT)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 28 (53.57%)	4 / 33 (12.12%)	
Injury, poisoning and procedural complications			
FALL			
subjects affected / exposed	6 / 28 (21.43%)	2 / 33 (6.06%)	
occurrences (all)	6	3	
PROCEDURAL PAIN			
subjects affected / exposed	3 / 28 (10.71%)	0 / 33 (0.00%)	
occurrences (all)	3	0	
Nervous system disorders			
PARKINSON'S DISEASE			
subjects affected / exposed	1 / 28 (3.57%)	2 / 33 (6.06%)	
occurrences (all)	1	2	
General disorders and administration site conditions			
DRUG WITHDRAWAL SYNDROME			
subjects affected / exposed	2 / 28 (7.14%)	0 / 33 (0.00%)	
occurrences (all)	2	0	

Psychiatric disorders DEPRESSION subjects affected / exposed occurrences (all) ANXIETY subjects affected / exposed occurrences (all)	 2 / 28 (7.14%) 2 2 / 28 (7.14%) 2	 1 / 33 (3.03%) 1 0 / 33 (0.00%) 0	
Gastrointestinal disorders ABDOMINAL PAIN subjects affected / exposed occurrences (all) DIARRHOEA subjects affected / exposed occurrences (all)	 2 / 28 (7.14%) 2 2 / 28 (7.14%) 2	 0 / 33 (0.00%) 0 0 / 33 (0.00%) 0	
Musculoskeletal and connective tissue disorders MUSCLE SPASMS subjects affected / exposed occurrences (all)	 2 / 28 (7.14%) 2	 0 / 33 (0.00%) 0	
Infections and infestations URINARY TRACT INFECTION subjects affected / exposed occurrences (all)	 2 / 28 (7.14%) 2	 0 / 33 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 May 2016	• Changed the study duration from 26 weeks to 12 weeks • Removed the exclusion criterion for excluding patients previously treated with continuous subcutaneous apomorphine infusion • Added language for additional analysis to provide evidence on the construct validity of the UDysRS

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported