



Clinical trial results:

Open-Label Continuation Treatment Study with Levodopa-Carbidopa Intestinal Gel in Subjects with Advanced Parkinson's Disease and Severe Motor-Fluctuations Who Have Exhibited a Persistent and Positive Effect to Treatment in Previous Studies

Summary

EudraCT number	2008-001329-33
Trial protocol	PT CZ GB
Global end of trial date	30 November 2021

Results information

Result version number	v1 (current)
This version publication date	05 November 2022
First version publication date	05 November 2022

Trial information

Trial identification

Sponsor protocol code	S187.3.005
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00660673
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, 001 800-633-9110, abbvieclinicaltrials@abbvie.com
Scientific contact	Global Medical Services, AbbVie, 001 800-633-9110, 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	30 November 2021
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	30 November 2021
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 provide, under well-controlled conditions, continued access to LCIG treatment to subjects who had already participated in an open-label efficacy and safety study with the same treatment (Study S187-3-003 [2006-000578-53], Study S187-3-004 [2006-005186-18]), and in whom the need for such continuation is indicated, as confirmed by periodic evaluation, until the product becomes commercially available.

Protection of trial subjects:

Subject read and understood the information provided about the study and gave written permission.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 November 2009
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	Australia: 12
Country: Number of subjects enrolled	Canada: 11
Country: Number of subjects enrolled	Czechia: 22
Country: Number of subjects enrolled	Israel: 9
Country: Number of subjects enrolled	New Zealand: 10
Country: Number of subjects enrolled	Poland: 4
Country: Number of subjects enrolled	Portugal: 14
Country: Number of subjects enrolled	Russian Federation: 43
Country: Number of subjects enrolled	Thailand: 13
Country: Number of subjects enrolled	United Kingdom: 11
Country: Number of subjects enrolled	United States: 113
Worldwide total number of subjects	262
EEA total number of subjects	40

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)	133
From 65 to 84 years	129
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Enrollment began in November 2009 and was completed in October 2012. Participants were enrolled at 61 sites in 11 countries: Australia, Canada, Czech Republic, Israel, New Zealand, Poland, Portugal, the Russian Federation, Thailand, the United Kingdom, and the United States.

Pre-assignment

Screening details:

This study was an open-label extension study for participants with Parkinson's disease (PD) who had completed prior study S187.3.003 or S187.3.004. Participants were to receive continued access to levodopa-carbidopa intestinal gel (LCIG) in the extension study until treatment became commercially available in their home country.

Period 1

Period 1 title	LCIG Extension Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Levodopa-Carbidopa Intestinal Gel
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Arm description:

Participants received levodopa-carbidopa intestinal gel (LCIG), continuously administered through a percutaneous endoscopic gastrostomy with jejunal extension tube (PEG-J) directly into the jejunum via a portable pump during 16 hours of wakefulness.

Initial dosing was based on the dosing regimen that the participant received during the previous LCIG study. Dosing was individually optimized and adjusted as clinically indicated.

In addition to a morning dose (to prime the intestinal tube and rapidly achieve the therapeutic dose level) of 5 to 10 mL (100 to 200 mg levodopa), and the continuous infusion usually 2 to 6 mL/hour (40 to 120 mg levodopa/hour), participants were allowed to self-administer additional doses of LCIG to address immediate subjective needs (eg, deterioration of motor function).

Participants received LCIG until it became commercially available.

Arm type	Experimental
Investigational medicinal product name	Levodopa-Carbidopa Intestinal Gel
Investigational medicinal product code	
Other name	Duodopa®, Duopa®, Carbidopa/levodopa enteral suspension (CLES)
Pharmaceutical forms	Intestinal gel
Routes of administration	Gastroenteral use

Dosage and administration details:

LCIG is administered over approximately 16 waking hours.

Number of subjects in period 1	Levodopa-Carbidopa Intestinal Gel
Started	262
Completed	145
Not completed	117
Consent withdrawn by subject	22
Administrative	2
Adverse event, non-fatal	84

Protocol Violation	2
Lack of efficacy	7

Baseline characteristics

Reporting groups

Reporting group title	LCIG Extension Study
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Reporting group description: -

Reporting group values	LCIG Extension Study	Total	
Number of subjects	262	262	
Age categorical			
Units: Subjects			
< 65 years	133	133	
≥ 65 years	129	129	
Age continuous			
Units: years			
arithmetic mean	64.1		
standard deviation	± 8.9	-	
Gender categorical			
Units: Subjects			
Female	100	100	
Male	162	162	
Race			
Units: Subjects			
American Indian or Alaska Native	1	1	
Asian	21	21	
Black of African Heritage or African American	1	1	
Native Hawaiian or Other Pacific Islander	0	0	
White	239	239	

End points

End points reporting groups

Reporting group title	Levodopa-Carbidopa Intestinal Gel
Reporting group description:	
Participants received levodopa-carbidopa intestinal gel (LCIG), continuously administered through a percutaneous endoscopic gastrostomy with jejunal extension tube (PEG-J) directly into the jejunum via a portable pump during 16 hours of wakefulness.	
Initial dosing was based on the dosing regimen that the participant received during the previous LCIG study. Dosing was individually optimized and adjusted as clinically indicated.	
In addition to a morning dose (to prime the intestinal tube and rapidly achieve the therapeutic dose level) of 5 to 10 mL (100 to 200 mg levodopa), and the continuous infusion usually 2 to 6 mL/hour (40 to 120 mg levodopa/hour), participants were allowed to self-administer additional doses of LCIG to address immediate subjective needs (eg, deterioration of motor function).	
Participants received LCIG until it became commercially available.	
Subject analysis set title	Year 1
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants who received LCIG during Year 1 of the extension study.	
Subject analysis set title	Year 2
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants who received LCIG during Year 2 of the extension study.	
Subject analysis set title	Year 3
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants who received LCIG during Year 3 of the extension study.	
Subject analysis set title	Year 4
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants who received LCIG during Year 4 of the extension study.	
Subject analysis set title	Year 5
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants who received LCIG during Year 5 of the extension study.	
Subject analysis set title	Year 6
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants who received LCIG during Year 6 of the extension study.	
Subject analysis set title	Year 7
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants who received LCIG during Year 7 of the extension study.	
Subject analysis set title	Year 8
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants who received LCIG during Year 8 of the extension study.	
Subject analysis set title	Year 9
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants who received LCIG during Year 9 of the extension study.	
Subject analysis set title	Year 10
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants who received LCIG during Year 10 of the extension study.

Subject analysis set title	> Year 10
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants who received LCIG after Year 10 of the extension study.

Primary: Number of Participants With Treatment-emergent Adverse Events

End point title	Number of Participants With Treatment-emergent Adverse Events ^[1]
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End point description:

Treatment-emergent adverse events (TEAEs) are defined as adverse events (AEs) which started on or after the date of the first LCIG Infusion in this study and within 30 days of the date of the last PEG-J exposure.

At least possibly drug-related is defined as TEAEs assessed as having a "Possible," "Probable" or missing relationship to study drug.

Serious AEs included any untoward medical occurrence that resulted in death, was life-threatening, required inpatient hospitalization or prolongation of an existing hospitalization, resulted in persistent or significant disability/incapacity, or was a congenital anomaly/birth defect.

The severity of all AEs was characterized as mild, moderate or severe according to the following definitions:

Mild: usually transient and do not interfere with daily activities.

Moderate: low level of inconvenience or concern to the subject, may interfere with daily activities.

Severe: events interrupt the subject's usual daily activity.

End point type	Primary
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End point timeframe:

From first dose of LCIG in this study up to 30 days after the date of last PEG-J exposure; median duration of treatment was 1178 days, with a maximum of 4217 days (11.5 years).

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analyses were not conducted.

End point values	Levodopa-Carbidopa Intestinal Gel			
Subject group type	Reporting group			
Number of subjects analysed	262 ^[2]			
Units: participants				
Any treatment-emergent adverse event (TEAE)	253			
TEAE at least possibly related to study drug	219			
Serious TEAE	159			
Severe TEAE	152			
TEAE leading to premature study discontinuation	82			
TEAE leading to death	58			

Notes:

[2] - All participants who received LCIG in this extension study

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Device Complications

End point title	Number of Participants With Device Complications
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End point description:

Device complications include complications with the pump, intestinal tube, PEG-J or stoma.

End point type	Secondary
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End point timeframe:

From first dose of LCIG in this study up to 30 days after the date of last PEG-J exposure; median duration of treatment was 1178 days.

End point values	Levodopa-Carbidopa Intestinal Gel			
Subject group type	Reporting group			
Number of subjects analysed	262			
Units: participants				
Any device complication	244			
Device complication leading to tube replacement	183			
Device complication with associated adverse event	177			
Device complication with AE and tube replacement	43			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Sleep Attacks

End point title	Number of Participants With Sleep Attacks
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End point description:

Participants were asked whether they experienced any events in which they fell asleep suddenly or unexpectedly, including while engaged in some activity (e.g., eating/drinking, speaking, or driving) or at rest, with or without any previous warning of sleepiness. If yes, participants were asked if they suffered any "bad" outcome or problem from the falling asleep event.

End point type	Secondary
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End point timeframe:

Baseline (final assessment period of the previous open-label LCIG study) and every 6 months until final visit; median duration of treatment was 1178 days.

End point values	Levodopa-Carbidopa Intestinal Gel			
Subject group type	Reporting group			
Number of subjects analysed	262 ^[3]			
Units: participants				
Baseline: One or more sleep attacks	6			
Baseline: ≥ 1 sleep attacks with a bad outcome	0			
Post-baseline: One or more sleep attacks (N=255)	27			

Post-baseline: ≥ 1 sleep attacks with a bad outcome	3			
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Notes:

[3] - 255 participants had post-baseline sleep attack data

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Intense Impulsive Behavior

End point title	Number of Participants With Intense Impulsive Behavior
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End point description:

To monitor for the development of intense impulsive behavior the Minnesota Impulsive Disorder Interview (MIDI) was administered. The MIDI is a semi-structured clinical interview assessing pathological gambling, trichotillomania, kleptomania, pyromania, intermittent explosive disorder, compulsive buying, and compulsive sexual behavior.

End point type	Secondary
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End point timeframe:

Baseline (final assessment of the previous open-label LCIG study) and every 6 months until final visit; median duration of treatment was 1178 days.

End point values	Levodopa-Carbidopa Intestinal Gel			
Subject group type	Reporting group			
Number of subjects analysed	262 ^[4]			
Units: participants				
Baseline: Pathological Gambling	1			
Baseline: Trichotillomania	0			
Baseline: Kleptomania	0			
Baseline: Pyromania	0			
Baseline: Intermittent Explosive Disorder	0			
Baseline: Compulsive Buying	1			
Baseline: Compulsive Sexual Behavior	1			
Post-baseline: Pathological Gambling	1			
Post-baseline: Trichotillomania	0			
Post-baseline: Kleptomania	0			
Post-baseline: Pyromania	0			
Post-baseline: Intermittent Explosive Disorder	0			
Post-baseline: Compulsive Buying	2			
Post-baseline: Compulsive Sexual Behavior	14			

Notes:

[4] - 256 participants had post-baseline MIDI data

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Developed Melanoma

End point title	Number of Participants Who Developed Melanoma
End point description: A comprehensive assessment for the presence of melanoma was performed at least once a year by a dermatologist.	
End point type	Secondary
End point timeframe: Once per year during the study; median duration of treatment was 1178 days.	

End point values	Levodopa- Carbidopa Intestinal Gel			
Subject group type	Reporting group			
Number of subjects analysed	262			
Units: participants	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment-emergent Adverse Events of Special Interest (TE AESI)

End point title	Number of Participants With Treatment-emergent Adverse Events of Special Interest (TE AESI)
End point description: Adverse events of special interest (AESIs) were identified using standardized Medical Dictionary for Regulatory Activities (MedDRA) queries (SMQ) or company MedDRA queries (CMQs). The AESI in the following categories were identified on the basis of review of the clinical program and postmarketing observations where the treatment system is commercially available. - Procedure and device associated events; - Polyneuropathy, included preferred terms in either the peripheral neuropathy or GuillainBarre syndrome standardized MedDRA query (narrow search), such as polyneuropathy, decreased vibratory sense, peripheral neuropathy, peripheral sensory neuropathy, neuralgia, demyelinating polyneuropathy, and sensory disturbance; - Weight loss; - Cardiovascular fatalities; - Respiratory tract aspiration including aspiration pneumonia/pneumonitis.	
End point type	Secondary
End point timeframe: From first dose of LCIG in this study up to 30 days after the date of last PEG-J exposure; median duration of treatment was 1178 days, with a maximum of 4217 days (11.5 years).	

End point values	Levodopa-Carbidopa Intestinal Gel			
Subject group type	Reporting group			
Number of subjects analysed	262			
Units: participants				
TE AESI related to procedure and device	162			
TE AESI related to polyneuropathy	24			
TE AESI related to weight loss	53			
TE AESI related to cardiovascular fatalities	7			
TE AESI related to aspiration	71			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Any Suicidal Ideation or Behavior

End point title	Number of Participants With Any Suicidal Ideation or Behavior
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End point description:

The Columbia-Suicide Severity Rating Scale (C-SSRS) was implemented with Protocol Amendment 3 (20 March 2012) in order to assess suicidal behavior and ideation.

Suicidal ideation includes the wish to be dead, nonspecific active suicidal thoughts, active ideation without intent to act, active ideation with some intent to act, and active ideation with specific plan or intent. Suicidal behavior includes actual attempts, interrupted attempts, aborted attempts, completed suicide, and preparatory acts or behaviors.

The number of participants with affirmative responses on the C-SSRS at any time during the treatment period is reported.

End point type	Secondary
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End point timeframe:

Every 6 months (beginning with implementation of Protocol Amendment 3) until final visit; median duration of treatment was 1178 days.

End point values	Levodopa-Carbidopa Intestinal Gel			
Subject group type	Reporting group			
Number of subjects analysed	210 ^[5]			
Units: participants				
Any suicidal ideation or behavior	32			
Any suicidal ideation	30			
Any suicidal behavior	6			
Non-suicidal self-injurious behavior	1			

Notes:

[5] - All participants who received LCIG in this extension study with available C-SSRS data

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Potentially Clinically Significant Vital Sign Values

End point title	Number of Participants With Potentially Clinically Significant Vital Sign Values
End point description: A vital sign value was considered potentially clinically significant if it satisfied the pre-specified criteria presented in the table and was also more extreme than the participant's corresponding Baseline (BL) value. Vital signs included systolic blood pressure (SBP), diastolic blood pressure (DBP), orthostatic change in blood pressure (supine to standing) pulse rate, temperature, and weight.	
End point type	Secondary
End point timeframe: Baseline and every 6 months until final visit; median duration of treatment was 1178 days.	

End point values	Levodopa-Carbidopa Intestinal Gel			
Subject group type	Reporting group			
Number of subjects analysed	255 ^[6]			
Units: participants				
Supine SBP ≥ 180 mmHg and >40 mmHg increase from BL	6			
Supine SBP ≤ 90 mmHg and >30 mmHg decrease from BL	13			
Standing SBP ≥ 180 mmHg and >40 mmHg increase from BL	1			
Standing SBP ≤ 90 mmHg and >30 mmHg decrease from BL	26			
Orthostatic Change in SBP Decrease of ≥ 30 mmHg	73			
Supine DBP ≥ 105 mmHg and >30 mmHg increase from BL	2			
Supine DBP ≤ 50 mmHg and >30 mmHg decrease from BL	6			
Standing DBP ≥ 105 mmHg and >30 mmHg increase from BL	7			
Standing DBP ≤ 50 mmHg and >30 mmHg decrease from BL	14			
Orthostatic Change in DBP Decrease of ≥ 20 mmHg	45			
Supine Pulse ≥ 120 bpm and >30 bpm increase from BL	0			
Supine Pulse ≤ 50 bpm and >30 bpm decrease from BL	3			
Standing Pulse ≥ 120 bpm and >30 bpm increase from BL	5			
Standing Pulse ≤ 50 bpm and >30 bpm decrease from BL	4			
Temperature ≥ 38.3 and ≥ 1.1 increase from BL	0			
Weight $\geq 7\%$ increase from BL	36			
Weight $\geq 7\%$ decrease from BL	140			

Notes:

[6] - 254 subjects had standing BP and pulse, temp and weight data; 253 had orthostatic change in BP data.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Potentially Clinically Significant Hematology Laboratory Values

End point title	Number of Participants With Potentially Clinically Significant Hematology Laboratory Values
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End point description:

A laboratory value was considered potentially clinically significant if it satisfied the pre-specified criteria presented in the table and was also more extreme than the participant's corresponding baseline value. Hematology included red blood cell (RBC) count, white blood cell (WBC) count, haemoglobin, haematocrit, absolute neutrophil count (ANC), lymphocytes, eosinophils, platelets, monocytes, and mean corpuscular volume (MCV).

End point type	Secondary
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End point timeframe:

Baseline and every 6 months until final visit; median duration of treatment was 1178 days.

End point values	Levodopa-Carbidopa Intestinal Gel			
Subject group type	Reporting group			
Number of subjects analysed	196 ^[7]			
Units: participants				
RBC < 2.0 10 ¹² /L (Female); < 2.5 10 ¹² /L (Male)	0			
Haemoglobin < 90 g/L (Female); < 100 g/L (Male)	9			
Haematocrit < 30 % (Female); < 34 % (Male)	16			
White blood cells (WBC) < 2.8 10 ⁹ /L	3			
WBC > 16.0 10 ⁹ /L	2			
Absolute neutrophil count < 1.2 10 ⁹ /L	2			
Lymphocytes > 80 %	0			
Absolute lymphocyte count < 0.75 10 ⁹ /L	14			
Eosinophils > 10%	4			
Monocytes > 30%	1			
Platelet count < 95 10 ⁹ /L	2			
Platelet count > 700 10 ⁹ /L	0			
Mean corpuscular volume (MCV) < 60 fL	0			
MCV > 120 fL	0			

Notes:

[7] - 195 subjects had haematocrit, MCV and WBC differential post-baseline data; 194 had platelet data.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Potentially Clinically Significant Chemistry Laboratory Values

End point title	Number of Participants With Potentially Clinically Significant
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End point description:

A laboratory value was considered potentially clinically significant if it satisfied the pre-specified criteria presented in the table and was also more extreme than the participant's corresponding baseline value.
ULN = upper limit of normal

End point type	Secondary
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End point timeframe:

Baseline and every 6 months until final visit; median duration of treatment was 1178 days.

End point values	Levodopa-Carbidopa Intestinal Gel			
Subject group type	Reporting group			
Number of subjects analysed	198 ^[8]			
Units: participants				
Creatinine > 177 µmol/L	0			
Calcium < 1.75 mmol/L	1			
Calcium > 3.0 mmol/L	0			
Total bilirubin > 2 x ULN	0			
Aspartate aminotransferase (AST) > 3 x ULN	0			
Alanine aminotransferase (ALT) > 3 x ULN	0			
Gamma glutamyl-transferase (GGT) > 3 x ULN	5			
Lactate dehydrogenase (LDH) > 3 x ULN	0			
Alkaline phosphatase (ALP) > 400 U/L	0			
Creatine phosphokinase (CPK) > 3 x ULN	6			
Non-fasting glucose < 2.78 mmol/L	4			
Non-fasting glucose > 16.0 mmol/L	1			
Uric acid > 500 µmol/L (Female); > 590 µmol/L (Male)	0			
Blood urea nitrogen (BUN) > 10.8 mmol/L	11			
Cholesterol > 12.9 mmol/L	0			

Notes:

[8] - 197 subjects had LDH post-baseline data; 95 subjects had BUN post-baseline data.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Vitamin Levels Outside of the Normal Range

End point title	Number of Participants With Vitamin Levels Outside of the Normal Range
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End point description:

Special tests for vitamin deficiencies (folic acid, vitamin B6, vitamin B12, methylmalonic acid [MMA], and homocysteine) were implemented with Protocol Amendment 2 (27 July 2011). The number of participants with vitamin levels outside of the normal range at any time post-baseline is reported for each vitamin tested.

End point type	Secondary
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End point timeframe:

Every 6 months (beginning with implementation of Protocol Amendment 2) until final visit; median duration of treatment was 1178 days.

End point values	Levodopa-Carbidopa Intestinal Gel			
Subject group type	Reporting group			
Number of subjects analysed	214 ^[9]			
Units: participants				
Vitamin B12 < 148 pmol/L	22			
Vitamin B12 > 775 pmol/L	46			
Methylmalonic acid > 0.4 µmol/L	65			
Homocysteine < 3.7 µmol/L	1			
Homocysteine > 13.9 µmol/L	198			
Vitamin B6 < 20 nmol/L	155			
Vitamin B6 > 125 nmol/L	108			
Folic acid < 4.5 nmol/L	6			

Notes:

[9] - 212 subjects had vitamin B12 postbaseline data; 211 subjects had vitamin B6; and 213 had folate data

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Receiving Concomitant Anti-Parkinson's Disease Medications by Treatment Year

End point title	Number of Participants Receiving Concomitant Anti-Parkinson's Disease Medications by Treatment Year
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End point description:

Participants could use oral levodopa-carbidopa for scheduled or supplemental bedtime/overnight doses after the pump was disconnected for the night, or as rescue medication in case of acute deterioration caused by failure of the LCIG system such as tubes and/or the pump or the onset of an acute illness. The initiation of additional concomitant PD medication was allowed at the discretion of the Investigator if medically indicated.

End point type	Secondary
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End point timeframe:

Year 1, Year 2, Year 3, Year 4, Year 5, Year 6, Year 7, Year 8, Year 9, Year 10, > Year 10 (maximum time on treatment was approximately 11.5 years).

End point values	Year 1	Year 2	Year 3	Year 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	262	230	196	146
Units: participants				
No concomitant PD medications (LCIG only)	126	107	96	74
Concomitant oral levodopa/carbidopa	100	91	74	55
Other concomitant PD medications	36	32	26	17

End point values	Year 5	Year 6	Year 7	Year 8
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	96	59	44	38
Units: participants				
No concomitant PD medications (LCIG only)	52	38	33	28
Concomitant oral levodopa/carbidopa	37	16	9	8
Other concomitant PD medications	7	5	2	2

End point values	Year 9	Year 10	> Year 10	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	27	22	9	
Units: participants				
No concomitant PD medications (LCIG only)	21	17	8	
Concomitant oral levodopa/carbidopa	5	4	1	
Other concomitant PD medications	1	1	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Average Daily "Off" Time Based on the Parkinson's Disease Symptom Diary at End of Treatment

End point title	Change in Average Daily "Off" Time Based on the Parkinson's Disease Symptom Diary at End of Treatment
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End point description:

The PD symptom diary asks participants (or their caregivers) to indicate their status upon waking and every 30 minutes during their normal waking time according to the following categories: asleep, "off", "on" without dyskinesia, "on" with non-troublesome dyskinesia, or "on" with troublesome dyskinesia. "Off" time was defined as time when medication had worn off and was no longer providing benefit with regard to mobility, slowness, and stiffness.

PD diary times were normalized to a 16-hour waking day and averaged for the 3 days prior to each study visit.

A negative change for "off" time indicates improvement. The PD diary assessment was implemented with Protocol amendment 4 (December 2013) for participants at United States (US) sites only.

End point type	Secondary
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End point timeframe:

Prior to initial LCIG infusion (in the previous study, before the first LCIG infusion), Baseline (final assessment of the previous open-label LCIG study), and end of treatment; median duration of treatment was 1178 days.

End point values	Levodopa-Carbidopa Intestinal Gel			
Subject group type	Reporting group			
Number of subjects analysed	82 ^[10]			
Units: hours				
arithmetic mean (standard deviation)				
Change from initial LCIG infusion	-3.97 (± 2.86)			
Change from Baseline	-0.19 (± 2.19)			

Notes:

[10] - Participants who were enrolled in the US and had at least 1 efficacy assessment in the current study.

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Average Daily "On" Time Without Troublesome Dyskinesia Based on the Parkinson's Disease Symptom Diary at End of Treatment

End point title	Change in Average Daily "On" Time Without Troublesome Dyskinesia Based on the Parkinson's Disease Symptom Diary at End of Treatment
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End point description:

The PD diary asks participants (or their caregivers) to indicate their status upon waking and every 30 minutes during their normal waking time according to the following categories: asleep, "off", "on" without dyskinesia, "on" with non-troublesome dyskinesia, or "on" with troublesome dyskinesia. "On" time is when medication is providing benefit with regard to mobility, slowness and stiffness. Dyskinesia is involuntary twisting, turning movements which are an effect of medication and occur during "on" time. Non-troublesome dyskinesia does not interfere with function or cause meaningful discomfort.

"On" time without troublesome dyskinesia is the sum of "on" time without dyskinesia and "on" time with non-troublesome dyskinesia. PD diary times were normalized to a 16-hour waking day and averaged for the 3 days prior to each study visit. A positive change indicates improvement.

The PD diary was implemented with Protocol amendment 4 (December 2013) for participants at US sites only.

End point type	Secondary
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End point timeframe:

Prior to initial LCIG infusion (in the previous study, before the first LCIG infusion), Baseline (final assessment of the previous open-label LCIG study), and end of treatment; median duration of treatment was 1178 days.

End point values	Levodopa-Carbidopa Intestinal Gel			
Subject group type	Reporting group			
Number of subjects analysed	82 ^[11]			
Units: hours				
arithmetic mean (standard deviation)				
Change from initial LCIG infusion	3.86 (± 3.31)			
Change from Baseline	-0.51 (± 3.19)			

Notes:

[11] - Participants who were enrolled in the US and had at least 1 efficacy assessment in the current study

Statistical analyses

Secondary: Change in Average Daily "On" Time With Troublesome Dyskinesia Based on the Parkinson's Disease Symptom Diary at End of Treatment

End point title	Change in Average Daily "On" Time With Troublesome Dyskinesia Based on the Parkinson's Disease Symptom Diary at End of Treatment
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End point description:

The PD diary asks participants (or their caregivers) to indicate their status upon waking and every 30 minutes during their normal waking time according to the following categories: asleep, "off", "on" without dyskinesia, "on" with non-troublesome dyskinesia, or "on" with troublesome dyskinesia. "On" time is when medication is providing benefit with regard to mobility, slowness and stiffness. Dyskinesia is involuntary twisting, turning movements which are an effect of medication and occur during "on" time. Troublesome dyskinesia interferes with function or causes meaningful discomfort. PD diary times were normalized to a 16-hour waking day and averaged for the 3 days prior to each study visit. A positive change indicates improvement.

The PD diary was implemented with Protocol amendment 4 (December 2013) for participants at US sites only.

End point type	Secondary
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End point timeframe:

Prior to initial LCIG infusion (in the previous study, before the first LCIG infusion), Baseline (final assessment of the previous open-label LCIG study), and end of treatment; median duration of treatment was 1178 days.

End point values	Levodopa-Carbidopa Intestinal Gel			
Subject group type	Reporting group			
Number of subjects analysed	82 ^[12]			
Units: hours				
arithmetic mean (standard deviation)				
Change from initial LCIG infusion	0.12 (± 3.03)			
Change from Baseline	0.70 (± 2.66)			

Notes:

[12] - Participants who were enrolled in the US and had at least 1 efficacy assessment in the current study

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Unified Parkinson's Disease Rating Scale (UPDRS) Part I Score at End of Treatment

End point title	Change in Unified Parkinson's Disease Rating Scale (UPDRS) Part I Score at End of Treatment
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End point description:

The UPDRS is an Investigator-used rating tool to follow the longitudinal course of PD. It is made up of the following sections:

I) Mentation, Behavior, and Mood; II) Activities of Daily Living; III) Motor Examinations; IV) Complications of Therapy sections (including dyskinesias).

The Part I Score is the sum of the answers to the 4 questions that comprise Part I, each of which are measured on a 5-point scale (0-4). The Part I score ranges from 0-16 and higher scores are associated with more disability. A negative change from Baseline indicates improvement.

The UPDRS was implemented with Protocol amendment 4 (December 2013) for participants at US sites only.

End point type	Secondary
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End point timeframe:

Prior to initial LCIG infusion (in the previous study, before the first LCIG infusion), Baseline (final assessment of the previous open-label LCIG study), and end of treatment; median duration of treatment was 1178 days.

End point values	Levodopa-Carbidopa Intestinal Gel			
Subject group type	Reporting group			
Number of subjects analysed	82 ^[13]			
Units: score on a scale				
arithmetic mean (standard deviation)				
Change from initial LCIG infusion	1.51 (± 2.83)			
Change from Baseline	1.46 (± 2.29)			

Notes:

[13] - 79 subjects had available data for change from initial LCIG infusion.

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Unified Parkinson's Disease Rating Scale (UPDRS) Part II Score at End of Treatment

End point title	Change in Unified Parkinson's Disease Rating Scale (UPDRS) Part II Score at End of Treatment
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End point description:

The UPDRS is an Investigator-used rating tool to follow the longitudinal course of PD. It is made up of the following sections:

I) Mentation, Behavior, and Mood; II) Activities of Daily Living; III) Motor Examinations; IV) Complications of Therapy sections (including dyskinesias).

The Part II score is the sum of the answers to the 13 questions that comprise Part II, each of which are measured on a 5-point scale (0-4). The Part II score ranges from 0-52 and higher scores are associated with more disability. A negative change from Baseline indicates improvement.

The UPDRS was implemented with Protocol amendment 4 (December 2013) for participants at US sites only.

End point type	Secondary
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End point timeframe:

Prior to initial LCIG infusion (in the previous study, before the first LCIG infusion), Baseline (final assessment of the previous open-label LCIG study), and end of treatment; median duration of treatment was 1178 days.

End point values	Levodopa-Carbidopa Intestinal Gel			
Subject group type	Reporting group			
Number of subjects analysed	82 ^[14]			
Units: score on a scale				
arithmetic mean (standard deviation)				
Change from initial LCIG infusion	3.04 (± 7.76)			
Change from Baseline	6.11 (± 5.48)			

Notes:

[14] - 79 subjects had change from initial LCIG infusion data.

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Unified Parkinson's Disease Rating Scale (UPDRS) Part III Score at End of Treatment

End point title	Change in Unified Parkinson's Disease Rating Scale (UPDRS) Part III Score at End of Treatment
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End point description:

The UPDRS is an Investigator-used rating tool to follow the longitudinal course of PD. It is made up of the following sections:

I) Mentation, Behavior, and Mood; II) Activities of Daily Living; III) Motor Examinations; IV)

Complications of Therapy sections (including dyskinesias).

UPDRS Part III consists of 14 questions. Questions 20 - 26 are multi-part questions in that they are evaluated separately for multiple body parts. Counting each of these assessments leads to a total of 27 answers for Part III. The UPDRS Part III score is the sum of the 27 answers provided to the 14 Part III questions, each of which are measured on a 5-Point scale (0-4). The Part III score ranges from 0-108 and higher scores are associated with more disability. A negative change from Baseline indicates improvement.

The UPDRS was implemented with Protocol amendment 4 (December 2013) for participants at US sites only.

End point type	Secondary
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End point timeframe:

Prior to initial LCIG infusion (in the previous study, before the first LCIG infusion), Baseline (final assessment of the previous open-label LCIG study), and end of treatment; median duration of treatment was 1178 days.

End point values	Levodopa-Carbidopa Intestinal Gel			
Subject group type	Reporting group			
Number of subjects analysed	82 ^[15]			
Units: score on a scale				
arithmetic mean (standard deviation)				
Change from initial LCIG infusion	4.51 (± 14.71)			
Change from Baseline	9.18 (± 10.63)			

Notes:

[15] - 79 subjects had change from initial LCIG infusion data.

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Unified Parkinson's Disease Rating Scale (UPDRS) Total Score at End of Treatment

End point title	Change in Unified Parkinson's Disease Rating Scale (UPDRS) Total Score at End of Treatment
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End point description:

The UPDRS is an Investigator-used rating tool to follow the longitudinal course of PD. It is made up of the following sections:

I) Mentation, Behavior, and Mood; II) Activities of Daily Living; III) Motor Examinations; IV)

Complications of Therapy sections (including dyskinesias).

The UPDRS total score is the sum of the responses to the 31 questions (44 answers) that comprise Parts I - III of the scale. The total score ranges from 0 - 176 with 176 representing the worst (total) disability, and 0 no disability. A negative change from Baseline indicates improvement.

The UPDRS was implemented with Protocol amendment 4 (December 2013) for participants at US sites only.

End point type	Secondary
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End point timeframe:

Prior to initial LCIG infusion (in the previous study, before the first LCIG infusion), Baseline (final assessment of the previous open-label LCIG study), and end of treatment; median duration of treatment was 1178 days.

End point values	Levodopa-Carbidopa Intestinal Gel			
Subject group type	Reporting group			
Number of subjects analysed	82 ^[16]			
Units: score on a scale				
arithmetic mean (standard deviation)				
Change from initial LCIG infusion	9.12 (± 20.91)			
Change from Baseline	16.82 (± 15.01)			

Notes:

[16] - 79 subjects had change from initial LCIG infusion data.

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Unified Parkinson's Disease Rating Scale (UPDRS) Part IV Score at End of Treatment

End point title	Change in Unified Parkinson's Disease Rating Scale (UPDRS) Part IV Score at End of Treatment
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End point description:

The UPDRS is an Investigator-used rating tool to follow the longitudinal course of PD. It is made up of the following sections:

I) Mentation, Behavior, and Mood; II) Activities of Daily Living; III) Motor Examinations; IV)

Complications of Therapy sections (including dyskinesias).

The UPDRS Part IV Score is the sum of all answers to the 11 questions that comprise Part IV, 4 of which are measured on a 5-point scale (0 – 4) and 7 which are measured on a 2-point scale (0 – 1). The Part IV score ranges from 0 – 23 and higher scores are associated with more disability. A negative change from Baseline indicates improvement.

The UPDRS was implemented with Protocol amendment 4 (December 2013) for participants at US sites only.

End point type	Secondary
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End point timeframe:

Prior to initial LCIG infusion (in the previous study, before the first LCIG infusion), Baseline (final assessment of the previous open-label LCIG study), and end of treatment; median duration of treatment was 1178 days.

End point values	Levodopa-Carbidopa Intestinal Gel			
Subject group type	Reporting group			
Number of subjects analysed	82 ^[17]			
Units: score on a scale				
arithmetic mean (standard deviation)				
Change from initial LCIG infusion	-2.27 (± 3.70)			
Change from Baseline	0.77 (± 2.86)			

Notes:

[17] - 79 subjects had change from initial LCIG infusion data.

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Unified Parkinson's Disease Rating Scale (UPDRS) Part IV Dyskinesia Score at End of Treatment

End point title	Change in Unified Parkinson's Disease Rating Scale (UPDRS) Part IV Dyskinesia Score at End of Treatment
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End point description:

The UPDRS is an Investigator-used rating tool to follow the longitudinal course of PD. It is made up of the following sections:

I) Mentation, Behavior, and Mood; II) Activities of Daily Living; III) Motor Examinations; IV)

Complications of Therapy sections (including dyskinesias); and

The UPDRS Part IV Dyskinesia Score is the sum of Questions 32 (What proportion of the waking day are dyskinesias present?), 33 (How disabling are the dyskinesias?), and 34 (How painful are the dyskinesias?) on UPDRS Part IV, each of which are measured on a 5-point scale (0-4). The Part IV dyskinesia score ranges from 0 - 12 and higher scores are associated with more disability. A negative change from Baseline indicates improvement.

The UPDRS was implemented with Protocol amendment 4 (December 2013) for participants at US sites only.

End point type	Secondary
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End point timeframe:

Prior to initial LCIG infusion (in the previous study, before the first LCIG infusion), Baseline (final assessment of the previous open-label LCIG study), and end of treatment; median duration of treatment was 1178 days.

End point values	Levodopa-Carbidopa Intestinal Gel			
Subject group type	Reporting group			
Number of subjects analysed	82 ^[18]			
Units: score on a scale				
arithmetic mean (standard deviation)				
Change from initial LCIG infusion	-0.19 (± 2.55)			
Change from Baseline	0.55 (± 1.86)			

Notes:

[18] - 79 subjects had change from initial LCIG infusion data.

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Parkinson's Disease Questionnaire (PDQ-39) Scores at End of Treatment

End point title	Change in Parkinson's Disease Questionnaire (PDQ-39) Scores at End of Treatment
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End point description:

The PDQ-39 is a self-administered questionnaire that comprises 39 items addressing the following 8 domains of health that patients consider to be adversely affected by the disease:

- Mobility (e.g., fear of falling when walking) - 10 questions;
- Activities of daily living (ADL) - 6 questions;
- Emotional well-being (EMO; e.g., feelings of isolation) - 6 questions;
- Stigma (e.g., social embarrassment) - 4 questions;
- Social support (SOC) - 3 questions;
- Cognition - 4 questions;
- Communication (COM) - 3 questions;
- Bodily discomfort (BOD) - 3 questions.

Each question is answered on a 5-point scale from 0 (Never) to 4 (Always / Cannot Do At All). Domain scores are calculated by summing the answers to the questions in the domain and then converting to a scale from 0 to 100. Higher scores are associated with the more severe symptoms of the disease such as tremor and stiffness. The PDQ-39 summary index includes responses to all 39 items. A negative change indicates improvement.

End point type	Secondary
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End point timeframe:

Prior to initial LCIG infusion (in the previous study, before the first LCIG infusion), Baseline (final assessment of the previous open-label LCIG study), and end of treatment; median duration of treatment was 1178 days.

End point values	Levodopa-Carbidopa Intestinal Gel			
Subject group type	Reporting group			
Number of subjects analysed	102 ^[19]			
Units: score on a scale				
arithmetic mean (standard deviation)				
Summary Index: Change from initial LCIG infusion	-1.46 (± 16.98)			
Summary Index: Change from Baseline	6.83 (± 13.14)			
Mobility Domain: Change from initial LCIG infusion	-2.08 (± 27.98)			
Mobility Domain: Change from Baseline	12.01 (± 21.81)			
ADL Domain: Change from initial LCIG infusion	-1.55 (± 28.40)			
ADL Domain: Change from Baseline	9.35 (± 20.40)			
EMO Domain: Change from initial LCIG infusion	-0.58 (± 19.31)			

EMO Domain: Change from Baseline	2.53 (± 16.95)			
Stigma Domain: Change from initial LCIG infusion	-9.50 (± 22.49)			
Stigma Domain: Change from Baseline	-0.18 (± 19.52)			
SOC Domain: Change from initial LCIG infusion	3.59 (± 19.54)			
SOC Domain: Change from Baseline	2.25 (± 17.88)			
Cognition Domain: Change from initial LCIG infusio	1.78 (± 19.52)			
Cognition Domain: Change from Baseline	6.56 (± 19.63)			
COM Domain: Change from initial LCIG infusion	3.19 (± 23.01)			
COM Domain: Change from Baseline	8.17 (± 19.27)			
BOD Domain: Change from initial LCIG infusion	-4.74 (± 24.61)			
BOD Domain: Change from Baseline	5.64 (± 19.70)			

Notes:

[19] - 101 subjects had EMO Domain and SOC Domain change from initial LCIG infusion data available

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of LCIG in this study up to 30 days after the date of last PEG-J exposure; median duration of treatment was 1178 days, and maximum was 4217 days (11.5 years).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups

Reporting group title	Levodopa-Carbidopa Intestinal Gel
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Reporting group description:

Participants received LCIG continuously administered through a PEG-J directly into the jejunum via a portable pump during 16 hours of wakefulness.

Initial dosing was based on the dosing regimen that the participant received during the previous LCIG study. Dosing was individually optimized and adjusted as clinically indicated.

In addition to a morning dose (to prime the intestinal tube and rapidly achieve the therapeutic dose level) of 5 to 10 mL (100 to 200 mg levodopa), and the continuous infusion usually 2 to 6 mL/hour (40 to 120 mg levodopa/hour), participants were allowed to self-administer additional doses of LCIG to address immediate subjective needs (eg, deterioration of motor function).

Participants received LCIG until it became commercially available.

Serious adverse events	Levodopa-Carbidopa Intestinal Gel		
Total subjects affected by serious adverse events			
subjects affected / exposed	159 / 262 (60.69%)		
number of deaths (all causes)	59		
number of deaths resulting from adverse events	58		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
ACUTE LEUKAEMIA			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
COLON CANCER			
subjects affected / exposed	2 / 262 (0.76%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 1		
LUNG ADENOCARCINOMA			

subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
MALIGNANT MELANOMA			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
PERIPHERAL T-CELL LYMPHOMA UNSPECIFIED			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
RECTAL CANCER			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Vascular disorders			
CIRCULATORY COLLAPSE			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
DEEP VEIN THROMBOSIS			
subjects affected / exposed	2 / 262 (0.76%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
HYPOTENSION			
subjects affected / exposed	2 / 262 (0.76%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
HYPOVOLAEMIC SHOCK			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
SHOCK HAEMORRHAGIC			

subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
ORTHOSTATIC HYPOTENSION			
subjects affected / exposed	2 / 262 (0.76%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
SUBGALEAL HAEMATOMA			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
COMPLICATION OF DEVICE INSERTION			
subjects affected / exposed	14 / 262 (5.34%)		
occurrences causally related to treatment / all	24 / 24		
deaths causally related to treatment / all	0 / 0		
CHEST PAIN			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
DEATH			
subjects affected / exposed	13 / 262 (4.96%)		
occurrences causally related to treatment / all	0 / 13		
deaths causally related to treatment / all	0 / 13		
DEVICE DISLOCATION			
subjects affected / exposed	6 / 262 (2.29%)		
occurrences causally related to treatment / all	4 / 8		
deaths causally related to treatment / all	0 / 0		
DEVICE BREAKAGE			

subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
DEVICE MATERIAL ISSUE				
subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
GENERAL PHYSICAL HEALTH DETERIORATION				
subjects affected / exposed	2 / 262 (0.76%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
DEVICE OCCLUSION				
subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
MALAISE				
subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
MEDICAL DEVICE SITE REACTION				
subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
MULTI-ORGAN FAILURE				
subjects affected / exposed	2 / 262 (0.76%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
NECROSIS				
subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
PYREXIA				

subjects affected / exposed	2 / 262 (0.76%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
NON-CARDIAC CHEST PAIN			
subjects affected / exposed	2 / 262 (0.76%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
SUDDEN DEATH			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Reproductive system and breast disorders			
BENIGN PROSTATIC HYPERPLASIA			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
PELVIC HAEMATOMA			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
PROSTATOMEGALY			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
ACUTE RESPIRATORY FAILURE			
subjects affected / exposed	3 / 262 (1.15%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
ASPIRATION			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

ATELECTASIS				
subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
BRONCHITIS CHRONIC				
subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
CHOKING				
subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
CHRONIC OBSTRUCTIVE PULMONARY DISEASE				
subjects affected / exposed	2 / 262 (0.76%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
DYSPNOEA				
subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
HAEMOPTYSIS				
subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
HAEMOTHORAX				
subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
HYPOXIA				
subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
LUNG INFILTRATION				

subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
PLEURAL EFFUSION			
subjects affected / exposed	4 / 262 (1.53%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 1		
PLEURAL DISORDER			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
PULMONARY EMBOLISM			
subjects affected / exposed	4 / 262 (1.53%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 2		
PNEUMONIA ASPIRATION			
subjects affected / exposed	9 / 262 (3.44%)		
occurrences causally related to treatment / all	2 / 12		
deaths causally related to treatment / all	0 / 2		
PULMONARY OEDEMA			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
RESPIRATORY ACIDOSIS			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
RESPIRATORY DISTRESS			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
RESPIRATORY ARREST			

subjects affected / exposed	2 / 262 (0.76%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
RESPIRATORY FAILURE			
subjects affected / exposed	5 / 262 (1.91%)		
occurrences causally related to treatment / all	1 / 5		
deaths causally related to treatment / all	0 / 3		
Psychiatric disorders			
AFFECTIVE DISORDER			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
ABNORMAL BEHAVIOUR			
subjects affected / exposed	2 / 262 (0.76%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
CONFUSIONAL STATE			
subjects affected / exposed	2 / 262 (0.76%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
ANXIETY			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
AGGRESSION			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
DELIRIUM			
subjects affected / exposed	2 / 262 (0.76%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
DOPAMINE DYSREGULATION SYNDROME			

subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
HALLUCINATION				
subjects affected / exposed	2 / 262 (0.76%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
MENTAL DISORDER DUE TO A GENERAL MEDICAL CONDITION				
subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
MENTAL STATUS CHANGES				
subjects affected / exposed	3 / 262 (1.15%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
SLEEP ATTACKS				
subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
PSYCHOTIC DISORDER				
subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
PARANOIA				
subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
SUICIDAL IDEATION				
subjects affected / exposed	2 / 262 (0.76%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
SUICIDE ATTEMPT				

subjects affected / exposed	2 / 262 (0.76%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Investigations			
BLOOD MAGNESIUM DECREASED			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
BLOOD POTASSIUM DECREASED			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
HAEMOGLOBIN DECREASED			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
HAEMATOCRIT DECREASED			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
HEART RATE DECREASED			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
PLATELET COUNT DECREASED			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
OXYGEN SATURATION DECREASED			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
URINE OUTPUT DECREASED			

subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
WEIGHT DECREASED			
subjects affected / exposed	8 / 262 (3.05%)		
occurrences causally related to treatment / all	7 / 10		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
CONCUSSION			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
ANAEMIA POSTOPERATIVE			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
CONTUSION			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
EXTRADURAL HAEMATOMA			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
FACIAL BONES FRACTURE			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
FEMORAL NECK FRACTURE			
subjects affected / exposed	2 / 262 (0.76%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
FALL			

subjects affected / exposed	13 / 262 (4.96%)		
occurrences causally related to treatment / all	3 / 15		
deaths causally related to treatment / all	0 / 1		
FEMUR FRACTURE			
subjects affected / exposed	4 / 262 (1.53%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
HEAD INJURY			
subjects affected / exposed	2 / 262 (0.76%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
HEAT STROKE			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
HIP FRACTURE			
subjects affected / exposed	5 / 262 (1.91%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
HUMERUS FRACTURE			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
JOINT INJURY			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
MEDICATION ERROR			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
LUMBAR VERTEBRAL FRACTURE			

subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
PERIPROSTHETIC FRACTURE				
subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
PERIPROSTHETIC OSTEOLYSIS				
subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
POST PROCEDURAL HAEMORRHAGE				
subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
POST-TRAUMATIC PAIN				
subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
PROCEDURAL PAIN				
subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
PROCEDURAL SITE REACTION				
subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
PUBIS FRACTURE				
subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
SUBDURAL HAEMATOMA				

subjects affected / exposed	2 / 262 (0.76%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
RIB FRACTURE			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
TIBIA FRACTURE			
subjects affected / exposed	2 / 262 (0.76%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
WOUND DEHISCENCE			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
ANGINA PECTORIS			
subjects affected / exposed	2 / 262 (0.76%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
ACUTE MYOCARDIAL INFARCTION			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
ATRIAL FIBRILLATION			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
CARDIAC ARREST			
subjects affected / exposed	3 / 262 (1.15%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	1 / 2		
CARDIAC FAILURE			

subjects affected / exposed	2 / 262 (0.76%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
CARDIAC FAILURE ACUTE			
subjects affected / exposed	3 / 262 (1.15%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 3		
CARDIOPULMONARY FAILURE			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
CARDIO-RESPIRATORY ARREST			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
CARDIAC FAILURE CONGESTIVE			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
CARDIAC FAILURE CHRONIC			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
EXTRASYSTOLES			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
MYOCARDIAL INFARCTION			
subjects affected / exposed	4 / 262 (1.53%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 3		
SICK SINUS SYNDROME			

subjects affected / exposed	2 / 262 (0.76%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
SUPRAVENTRICULAR TACHYCARDIA			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
VENTRICULAR TACHYCARDIA			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
CEREBRAL HAEMORRHAGE			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
BALANCE DISORDER			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
CEREBRAL ISCHAEMIA			
subjects affected / exposed	2 / 262 (0.76%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
COGNITIVE DISORDER			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
CEREBROVASCULAR ACCIDENT			
subjects affected / exposed	2 / 262 (0.76%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
CONVULSION			

subjects affected / exposed	2 / 262 (0.76%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 1			
DEMENTIA				
subjects affected / exposed	2 / 262 (0.76%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
DEPRESSED LEVEL OF CONSCIOUSNESS				
subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
ISCHAEMIC STROKE				
subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
EPILEPSY				
subjects affected / exposed	2 / 262 (0.76%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
LOSS OF CONSCIOUSNESS				
subjects affected / exposed	3 / 262 (1.15%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
MENTAL IMPAIRMENT				
subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
METABOLIC ENCEPHALOPATHY				
subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
MONOPLEGIA				

subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
MYOCLONUS				
subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
NEUROPATHY PERIPHERAL				
subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
PARKINSON'S DISEASE				
subjects affected / exposed	8 / 262 (3.05%)			
occurrences causally related to treatment / all	0 / 8			
deaths causally related to treatment / all	0 / 3			
ON AND OFF PHENOMENON				
subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
PARKINSONIAN CRISIS				
subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
RUPTURED CEREBRAL ANEURYSM				
subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
POLYNEUROPATHY				
subjects affected / exposed	2 / 262 (0.76%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
SCIATICA				

subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
SEDATION			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
SYNCOPE			
subjects affected / exposed	4 / 262 (1.53%)		
occurrences causally related to treatment / all	4 / 5		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	5 / 262 (1.91%)		
occurrences causally related to treatment / all	3 / 5		
deaths causally related to treatment / all	0 / 0		
HAEMORRHAGIC ANAEMIA			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
CATARACT			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
VENOUS STASIS RETINOPATHY			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	5 / 262 (1.91%)		
occurrences causally related to treatment / all	2 / 5		
deaths causally related to treatment / all	0 / 0		

ABDOMINAL DISCOMFORT				
subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
BEZOAR				
subjects affected / exposed	4 / 262 (1.53%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	0 / 0			
DIARRHOEA				
subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
CONSTIPATION				
subjects affected / exposed	3 / 262 (1.15%)			
occurrences causally related to treatment / all	2 / 5			
deaths causally related to treatment / all	0 / 0			
DUODENAL ULCER				
subjects affected / exposed	4 / 262 (1.53%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	0 / 0			
GASTROINTESTINAL HAEMORRHAGE				
subjects affected / exposed	2 / 262 (0.76%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
GASTRIC ULCER				
subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
DYSPHAGIA				
subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
GIANT CELL EPULIS				

subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
INGUINAL HERNIA				
subjects affected / exposed	3 / 262 (1.15%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
ILEUS PARALYTIC				
subjects affected / exposed	2 / 262 (0.76%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
INTESTINAL DILATATION				
subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
INTESTINAL ISCHAEMIA				
subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
INTUSSUSCEPTION				
subjects affected / exposed	2 / 262 (0.76%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
INTESTINAL OBSTRUCTION				
subjects affected / exposed	3 / 262 (1.15%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
JEJUNAL ULCER				
subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
MELAENA				

subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
OBSTRUCTION GASTRIC				
subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
OESOPHAGEAL FOOD IMPACTION				
subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
OESOPHAGEAL ULCER HAEMORRHAGE				
subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
OESOPHAGITIS				
subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
PANCREATITIS				
subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
PANCREATITIS ACUTE				
subjects affected / exposed	3 / 262 (1.15%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
PERITONITIS				
subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
PNEUMOPERITONEUM				

subjects affected / exposed	2 / 262 (0.76%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
SMALL INTESTINAL HAEMORRHAGE			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
RECTAL PROLAPSE			
subjects affected / exposed	2 / 262 (0.76%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
SMALL INTESTINAL OBSTRUCTION			
subjects affected / exposed	2 / 262 (0.76%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
UPPER GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
VOMITING			
subjects affected / exposed	2 / 262 (0.76%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
VOLVULUS			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
CHOLANGITIS SCLEROSING			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
BILE DUCT STONE			

subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
DECUBITUS ULCER			
subjects affected / exposed	3 / 262 (1.15%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
EXCESSIVE GRANULATION TISSUE			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
BLADDER NECK OBSTRUCTION			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
HAEMATURIA			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
RENAL FAILURE ACUTE			
subjects affected / exposed	2 / 262 (0.76%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
NEPHROLITHIASIS			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
STRESS URINARY INCONTINENCE			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
URINARY RETENTION			

subjects affected / exposed	3 / 262 (1.15%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
BACK PAIN			
subjects affected / exposed	2 / 262 (0.76%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
ARTHRALGIA			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
BONE PAIN			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
MOBILITY DECREASED			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
CAMPTOCORMIA			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
MUSCULAR WEAKNESS			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
OSTEOARTHRITIS			
subjects affected / exposed	5 / 262 (1.91%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
MUSCULOSKELETAL CHEST PAIN			

subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
OSTEOCHONDROSIS			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
PAIN IN EXTREMITY			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
PATHOLOGICAL FRACTURE			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
SPINAL COLUMN STENOSIS			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
SCOLIOSIS			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
ABDOMINAL ABSCESS			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
ABSCESS LIMB			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
BRONCHITIS			

subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
APPENDICITIS			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
BRONCHOPNEUMONIA			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
CATHETER SITE INFECTION			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
CELLULITIS			
subjects affected / exposed	2 / 262 (0.76%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
CORONA VIRUS INFECTION			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
DEVICE RELATED INFECTION			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
OSTEOMYELITIS			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
GANGRENE			

subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
LOBAR PNEUMONIA				
subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
PELVIC ABSCESS				
subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
PNEUMONIA				
subjects affected / exposed	20 / 262 (7.63%)			
occurrences causally related to treatment / all	0 / 23			
deaths causally related to treatment / all	0 / 7			
POSTOPERATIVE WOUND INFECTION				
subjects affected / exposed	9 / 262 (3.44%)			
occurrences causally related to treatment / all	11 / 11			
deaths causally related to treatment / all	0 / 0			
POST PROCEDURAL SEPSIS				
subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
PYELONEPHRITIS				
subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
PYELONEPHRITIS ACUTE				
subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
PYOTHORAX				

subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
RESPIRATORY TRACT INFECTION				
subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
SEPSIS				
subjects affected / exposed	3 / 262 (1.15%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 2			
SEPTIC SHOCK				
subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
STAPHYLOCOCCAL BACTERAEemia				
subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
URINARY TRACT INFECTION				
subjects affected / exposed	5 / 262 (1.91%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 0			
WOUND INFECTION PSEUDOMONAS				
subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
WOUND INFECTION				
subjects affected / exposed	1 / 262 (0.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
WOUND INFECTION STAPHYLOCOCCAL				

subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
CACHEXIA			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
DEHYDRATION			
subjects affected / exposed	4 / 262 (1.53%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
HYPERGLYCAEMIA			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
HYPONATRAEMIA			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
HYPOKALAEMIA			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
MALNUTRITION			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
VITAMIN B6 DEFICIENCY			
subjects affected / exposed	1 / 262 (0.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Levodopa-Carbidopa Intestinal Gel		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	223 / 262 (85.11%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps) BASAL CELL CARCINOMA			
subjects affected / exposed	17 / 262 (6.49%)		
occurrences (all)	22		
Vascular disorders ORTHOSTATIC HYPOTENSION			
subjects affected / exposed	15 / 262 (5.73%)		
occurrences (all)	19		
General disorders and administration site conditions COMPLICATION OF DEVICE INSERTION			
subjects affected / exposed	19 / 262 (7.25%)		
occurrences (all)	25		
FATIGUE			
subjects affected / exposed	15 / 262 (5.73%)		
occurrences (all)	17		
Psychiatric disorders INSOMNIA			
subjects affected / exposed	31 / 262 (11.83%)		
occurrences (all)	35		
HALLUCINATION			
subjects affected / exposed	17 / 262 (6.49%)		
occurrences (all)	20		
ANXIETY			
subjects affected / exposed	24 / 262 (9.16%)		
occurrences (all)	27		
DEPRESSION			
subjects affected / exposed	32 / 262 (12.21%)		
occurrences (all)	35		
SLEEP ATTACKS			

subjects affected / exposed occurrences (all)	16 / 262 (6.11%) 19		
Investigations BLOOD HOMOCYSTEINE INCREASED subjects affected / exposed occurrences (all)	59 / 262 (22.52%) 64		
VITAMIN B6 DECREASED subjects affected / exposed occurrences (all)	71 / 262 (27.10%) 98		
VITAMIN B6 INCREASED subjects affected / exposed occurrences (all)	21 / 262 (8.02%) 25		
WEIGHT DECREASED subjects affected / exposed occurrences (all)	32 / 262 (12.21%) 36		
Injury, poisoning and procedural complications FALL subjects affected / exposed occurrences (all)	47 / 262 (17.94%) 70		
INCISION SITE ERYTHEMA subjects affected / exposed occurrences (all)	38 / 262 (14.50%) 46		
POST PROCEDURAL DISCHARGE subjects affected / exposed occurrences (all)	24 / 262 (9.16%) 31		
PROCEDURAL SITE REACTION subjects affected / exposed occurrences (all)	33 / 262 (12.60%) 47		
PROCEDURAL PAIN subjects affected / exposed occurrences (all)	28 / 262 (10.69%) 39		
Nervous system disorders BALANCE DISORDER subjects affected / exposed occurrences (all)	14 / 262 (5.34%) 17		
COGNITIVE DISORDER			

subjects affected / exposed occurrences (all) DYSKINESIA subjects affected / exposed occurrences (all) PARKINSON'S DISEASE subjects affected / exposed occurrences (all)	18 / 262 (6.87%) 18 28 / 262 (10.69%) 34 28 / 262 (10.69%) 38		
Blood and lymphatic system disorders ANAEMIA subjects affected / exposed occurrences (all)	18 / 262 (6.87%) 21		
Eye disorders CATARACT subjects affected / exposed occurrences (all)	13 / 262 (4.96%) 17		
Gastrointestinal disorders ABDOMINAL PAIN subjects affected / exposed occurrences (all) CONSTIPATION subjects affected / exposed occurrences (all) DIARRHOEA subjects affected / exposed occurrences (all) NAUSEA subjects affected / exposed occurrences (all)	22 / 262 (8.40%) 27 30 / 262 (11.45%) 39 24 / 262 (9.16%) 29 32 / 262 (12.21%) 40		
Skin and subcutaneous tissue disorders EXCESSIVE GRANULATION TISSUE subjects affected / exposed occurrences (all)	41 / 262 (15.65%) 67		
Musculoskeletal and connective tissue disorders ARTHRALGIA			

subjects affected / exposed occurrences (all) BACK PAIN subjects affected / exposed occurrences (all) MUSCULOSKELETAL PAIN subjects affected / exposed occurrences (all)	22 / 262 (8.40%) 31 21 / 262 (8.02%) 24 15 / 262 (5.73%) 20		
Infections and infestations URINARY TRACT INFECTION subjects affected / exposed occurrences (all) POSTOPERATIVE WOUND INFECTION subjects affected / exposed occurrences (all)	45 / 262 (17.18%) 86 55 / 262 (20.99%) 95		
Metabolism and nutrition disorders VITAMIN B6 DEFICIENCY subjects affected / exposed occurrences (all)	20 / 262 (7.63%) 22		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 October 2009	Amendment 1 implemented the following non-administrative changes: • The number of study sites has been changed from 20 to 30 to approximately 70 sites. The number of subjects (planned) was changed from approximately 100 to approximately 275 subjects. • Clarification was made in the inclusion criteria to ensure that enrolled subjects were: (1) completers of Study S187-3-003 or Study S187-3-004, and (2) in the principal investigator's opinion, would continue deriving benefit from long-term LCIG treatment. Clarification was also made in exclusion criteria to exclude those subjects who, in the investigator's opinion, had clinically significant findings (medical, laboratory, psychiatric, or surgical issues) that would interfere with the subject's long-term participation. • Changed the description of the total daily dose administration. Deleted "bolus" terminology in the morning bolus dose, the continuous maintenance dose, and extra bolus doses given as needed. • Replacement of PEG-J was changed: Previous device labeling recommended an annual replacement. The new tube labeling no longer required annual replacement. It was to be replaced on the basis of the judgment of the study gastroenterologist and performed as per local practice. A yearly check by the study gastroenterologist was to be included in the schedule of assessments including an evaluation of the tube to ensure the functionality of the tube. • The list of prohibited medication became less restrictive in recognition of the open-label nature of study treatment and due consideration given to the potential pharmacokinetic and pharmacodynamic interaction with LCIG. • The efficacy parameters, PD Diary, PDQ-39, and CGI-I, were removed from the clinical study protocol. A routine neurological exam was to be performed every 6 months to assess the continued benefit of LCIG treatment.
27 July 2011	Amendment 2 implemented the following non-administrative changes to ensure consistency within the protocol and LCIG program and to provide further clarifications of study design, assessments, and processes: • Updated inclusion criteria. • For Canada, subjects who either completed Study S187-3-004 or prematurely discontinued from Study S187-3-004 due to the study ending were allowed to participate in Study S187-3-005 with a minimum of 6 months of exposure to LCIG in Study S187-3-004. • The laboratory assessments were changed to include markers indicative of vitamin deficiencies that could predispose subjects to polyneuropathy: folic acid, vitamin B6, vitamin B12, MMA, and homocysteine. • Added a neurological examination. • Added Laboratory Evaluations table. • Specified a certified central laboratory, QLAB, to process and provide results for routine clinical laboratory tests throughout the study. Previously, no formal assessment of laboratory evaluations were scheduled, but were done as subject's condition mandated and was performed by a local lab as an element of routine care, and at the time of the subjects' discontinuation of the study.

20 March 2012	Amendment 3, dated 20 March 2012, implemented the following non-administrative changes for clarification and alignment with the sponsor's safety assessments: • Added Post Infusion Night-Time Treatment section. • Added Oral Rescue Medication section. • Added C-SSRS assessment.
17 December 2013	The purpose of Amendment 4 was to: • Add language to allow for a legally authorized representative (LAR) to give informed consent if a subject does not have the capacity to provide full informed consent. • Add language regarding transfer of subjects to commercial product to clarify the assessments that must be performed prior to subjects transferring to commercial product. • Update clinical device labeling information to clarify that storage conditions are not found on the device labels. • Update drug and device accountability information to clarify the process of drug and device accountability using the ClinPhone Drug Accountability (CDA) system. • Update language regarding Adverse Events of Special Interest (AESI) to clarify the use of questionnaires to collect follow-up information for both serious and nonserious AESIs meeting pre-defined criteria. • Add the following assessments: Parkinson's Disease Symptom Diary, UPDRS, PDQ-39, Dosing Diary at US sites only to allow for demonstration of maintenance of efficacy.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/29570853>