Clinical trial results:
A 12 Month, Dose-Level Blinded Study Investigating the Safety and Efficacy of CVT-301 (Levodopa Inhalation Powder) in Parkinson's Disease Patients With Motor Response Fluctuations (OFF Phenomena)

Summary

EudraCT number	2015-005626-19
Trial protocol	CZ ES
Global end of trial date	23 May 2018

Results information

Result version number	v1 (current)
This version publication date	13 June 2019
First version publication date	13 June 2019

Trial information

Trial identification

Sponsor protocol code	CVT-301-004E

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02242487
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Acorda Therapeutics
Sponsor organisation address	420 Saw Mill River Road, Ardsley, United States, 10502
Public contact	Charles Oh Senior Vice President Clinical Development, Acorda Therapeutics 420 Saw Mill River Road Ardsley, NY 10502, 011 914-326-5455, coh@acorda.com
Scientific contact	Charles Oh Senior Vice President Clinical Development, Acorda Therapeutics 420 Saw Mill River Road Ardsley, NY 10502, 011 914-326-5455, coh@acorda.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	03 December 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 May 2018
Global end of trial reached?	Yes
Global end of trial date	23 May 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To characterize the effects of CVT-301 on pulmonary safety, as assessed by spirometry (forced expiratory volume in 1 second [FEV1], forced vital capacity [FVC], and FEV1/FVC ratio) over a 12-month period.

Protection of trial subjects:

Conduct of the study must be approved by an appropriately constituted IRB or IEC. Approval is required for the study protocol, investigational drug brochure, protocol amendments, informed consent forms, patient information sheets, and advertising materials. For each study patient, written informed consent will be obtained prior to any protocol-related activities. As part of this procedure, the principal investigator or one of his/her associates must explain orally and in writing the nature, duration, and purpose of the study, and the action of the drug in such a manner that the patient is aware of the potential risks, inconveniences, or adverse effects that may occur. The patient should be informed that he/she may withdraw from the study at any time, and the patient will receive all information that is required by local regulations and ICH guidelines. The principal investigator will provide the Sponsor or its representative with a copy of the IRB/IEC-approved informed consent form prior to the start of the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 January 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 84
Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	Czech Republic: 8
Country: Number of subjects enrolled	Canada: 8
Country: Number of subjects enrolled	United States: 201
Worldwide total number of subjects	312
EEA total number of subjects	103

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	151
From 65 to 84 years	161
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Three hundred and twenty-five patients were randomized in study CVT-301-004E. Of these 325 patients, 237 were rollover patients from CVT-301-004, 43 were CVT- 301 naïve patients who were not previously enrolled in CVT-301 studies, 30 were rollover patients from the Observational Cohort in CVT-301-005, 9 were rollover patients from CVT-301-009.

Pre-assignment

Screening details:

* Idiophathic PD, aged 30-85 years * Modified Hoehn and Yahr scale 1-3 (ON state) * Daily OFF time > 2 hours/day (excluding morning OFF) * On a stabel DDI/LD regimen * Other PD medications stable >4 weeks prior to screening * UPDRS Part III >25% increase between ON and OFF at screening * Mini Mental Status Examination Score >25

Period 1

Period 1 title	12-month (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	CVT-301 Low Dose

Arm description:

60 mg of Levodopa

Arm type	Experimental
Investigational medicinal product name	CVT-301
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

60 mg (two capsules of 30 mg each) of Levodopa up to 5 times a day.

Arm title	CVT-301 High Dose

Arm description:

84 mg of Levodopa

Arm type	Experimental
Investigational medicinal product name	CVT-301
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

84 mg (two capsules of 42 mg each) up to 5 times a day.

Number of subjects in period 1	CVT-301 Low Dose	CVT-301 High Dose
Started	153	159
Completed	99	117
Not completed	54	42
Consent withdrawn by subject	29	14
Adverse event, non-fatal	13	15
Lost to follow-up	2	1
miscellaneous	4	6
Lack of efficacy	4	6
Protocol deviation	2	-

Baseline characteristics

Reporting groups	
Reporting group title	CVT-301 Low Dose
Reporting group description:	
60 mg of Levodopa	
Reporting group title	CVT-301 High Dose
Reporting group description:	
84 mg of Levodopa	

Reporting group values	CVT-301 Low Dose	CVT-301 High Dose	Total
Number of subjects	153	159	312
Age categorical			
There were 312 patients in the Safety Population. The mean age (SD) was 63.4 (8.55) years.			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	71	80	151
From 65-84 years	82	79	161
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	43	40	83
Male	110	119	229

Subject analysis sets	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
Of the 325 randomized patients, 312 patients were in the Safety population. There was approximately the same number of patients in each dose group.	
Subject analysis set title	ITT Population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Of the 325 randomized patients, 297 patients were in the ITT Population. There was approximately the same number of patients in each dose group.	

Reporting group values	Safety Population	ITT Population	
Number of subjects	312	297	
Age categorical			
There were 312 patients in the Safety Population. The mean age (SD) was 63.4 (8.55) years.			
Units: Subjects			
In utero	0	0	

Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	151	143	
From 65-84 years	161	154	
85 years and over	0	0	
Gender categorical			
Units: Subjects			
Female	229	83	
Male	83	214	

End points

End points reporting groups

Reporting group title	CVT-301 Low Dose
Reporting group description: 60 mg of Levodopa	
Reporting group title	CVT-301 High Dose
Reporting group description: 84 mg of Levodopa	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description: Of the 325 randomized patients, 312 patients were in the Safety population. There was approximately the same number of patients in each dose group.	
Subject analysis set title	ITT Population
Subject analysis set type	Intention-to-treat
Subject analysis set description: Of the 325 randomized patients, 297 patients were in the ITT Population. There was approximately the same number of patients in each dose group.	

Primary: Pulmonary safety of CVT-301 change from baseline for FEV1

End point title	Pulmonary safety of CVT-301 change from baseline for FEV1[1]
End point description: To characterize the effects of CVT-301 on pulmonary safety, as assessed by spirometry FEV1 (forced expiratory volume in 1 second) by treatment group and visit (TV). This study was a 12-month, dose-level blinded, multicenter study of 2 inhaled dose levels of CVT-301 for the treatment of up to 5 OFF periods per day in PD (Parkinson's Disease) patients experiencing motor fluctuations (OFF periods). Baseline is defined as the last non-missing assessment before the first dose of CVT-301 in study CVT-301-004 for the patients who received CVT-301 in CVT-301-004 and as the last non-missing assessment before the first dose of CVT-301 in CVT-301-004E for the rest of the patients.	
End point type	Primary
End point timeframe: Change from baseline at 52 weeks	

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: This was a Safety study and therefore reporting of pulmonary outcomes was descriptive.

End point values	CVT-301 Low Dose	CVT-301 High Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	159		
Units: liter				
log mean (standard deviation)				
Baseline (N=153 LD - 159 HD)	2.957 (± 0.6995)	3.117 (± 0.7735)		
TV3 (N=141 LD - 149 HD)	-0.059 (± 0.2321)	-0.078 (± 0.2108)		
TV4 (N=119 LD - 136 HD)	-0.057 (± 0.1999)	-0.058 (± 0.2136)		
TV5 (N=112 LD - 125 HD)	-0.076 (± 0.2155)	-0.052 (± 0.2096)		
TV6 (N=105 LD - 115 HD)	-0.086 (± 0.2238)	-0.097 (± 0.2230)		

Statistical analyses

No statistical analyses for this end point

Primary: Pulmonary Safety for CVT-301 change from baseline for FVC

End point title	Pulmonary Safety for CVT-301 change from baseline for FVC[2]

End point description:

To characterize the effects of CVT-301 on pulmonary safety, as assessed by spirometry FVC, (forced vital capacity ratio) by treatment group and visit (TV). This study was a 12-month, dose-level blinded, multicenter study of 2 inhaled dose levels of CVT-301 for the treatment of up to 5 OFF periods per day in PD patients experiencing motor fluctuations (OFF periods). Baseline is defined as the last non-missing assessment before the first dose of CVT-301 in study CVT-301-004 for the patients who received CVT-301 in CVT-301-004 and as the last non-missing assessment before the first dose of CVT-301 in CVT-301-004E for the rest of the patients.

End point type	Primary

End point timeframe:

Change from baseline at 52 weeks.

Notes:

[2] - 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: This was a Safety study and therefore reporting of pulmonary outcomes was descriptive.

End point values	CVT-301 Low Dose	CVT-301 High Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	159		
Units: Liter				
log mean (standard deviation)				
Baseline (N=153 LD - 159 HD)	3.840 (± 0.9047)	4.045 (± 0.9811)		
TV3 (N=141 LD - 149 HD)	-0.064 (± 0.2575)	-0.086 (± 0.2667)		
TV4 (N=119 LD - 136 HD)	-0.053 (± 0.2710)	-0.062 (± 0.2688)		
TV5 (N=112 LD - 125 HD)	-0.089 (± 0.3051)	-0.050 (± 0.2659)		
TV6 (N=105 LD - 115 HD)	-0.106 (± 0.2866)	-0.089 (± 0.2747)		

Statistical analyses

No statistical analyses for this end point

Primary: Pulmonary Safety for CVT-301 change from baseline for (FEV1/FVC)

End point title	Pulmonary Safety for CVT-301 change from baseline for (FEV1/FVC)[3]

End point description:

To characterize the effects of CVT-301 on pulmonary safety, as assessed by spirometry FEV1/FVC (FEV1 forced expiratory volume in 1 second and (FVC) forced vital capacity ratio). This study was a 12-month, dose-level blinded, multicenter study of 2 inhaled dose levels of CVT-301 for the treatment of up to 5 OFF periods per day in PD patients experiencing motor fluctuations (OFF periods). Baseline is defined as the last non-missing assessment before the first dose of CVT-301 in study CVT-301-004 for the patients who received CVT-301 in CVT-301-004 and as the last non-missing assessment before the first dose of CVT-301 in CVT-301-004E for the rest of the patients.

End point type	Primary

End point timeframe:

Change from baseline at 52 weeks

Notes:

[3] - 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: This was a Safety study and therefore reporting of pulmonary outcomes was descriptive.

End point values	CVT-301 Low Dose	CVT-301 High Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	159		
Units: Ratio %				
log mean (standard deviation)				
Baseline (N=153 LD - 159 HD)	77.2 (± 5.24)	77.2 (± 6.00)		
TV3 (N=141 LD - 149 HD)	-0.2 (± 3.35)	-0.3 (± 2.89)		
TV4 (N=119 LD - 136 HD)	-0.3 (± 3.64)	-0.3 (± 3.02)		
TV5 (N=112 LD - 125 HD)	-0.3 (± 2.75)	-0.3 (± 3.02)		
TV6 (N=105 LD - 115 HD)	-0.2 (± 3.36)	-0.7 (± 3.51)		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patients achieving resolution of an OFF to an ON state within 60 minutes.

End point title	Proportion of patients achieving resolution of an OFF to an ON state within 60 minutes.

End point description:

Proportion of patients achieving resolution of an OFF to an ON state within 60 minutes after study drug is administered in the clinic, and maintaining the ON state at 60 minutes after study drug administration (per the examiner’s subjective assessment).

End point type	Secondary

End point timeframe:

Up to 12 months

End point values	CVT-301 Low Dose	CVT-301 High Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144	153		
Units: Participants	98	128		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in OFF time.

End point title	Change from baseline in OFF time.

End point description:

Patient reported total daily OFF time and was assessed by the patient and recorded in the patient Diary. An "OFF state" is defined as the time when medication is not providing benefit with respect to mobility, slowness, and stiffness. OFF episodes may be heralded by non-motor symptoms (e.g., pain, anxiety) prior to the appearance of motor symptoms. Patients will record their ON and OFF states in their diaries at home. TV = Treatment group and visit.

End point type	Secondary

End point timeframe:

Change from baseline through 12 months duration of outpatient use.

End point values	CVT-301 Low Dose	CVT-301 High Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144	153		
Units: Hours				
least squares mean (standard error)				
TV2 (Week 4) (N=137 LD - 143HD)	-0.33 (± 0.221)	-0.55 (± 0.217)		
TV3 (Week 12) (N=133 LD - 139 HD)	-0.23 (± 0.232)	-0.38 (± 0.227)		
TV4 (Week 24) (N=114 LD - 130 HD)	-0.65 (± 0.235)	-0.73 (± 0.227)		
TV5 (Week 36) (N=102 LD - 116 HD)	-0.49 (± 0.238)	-0.92 (± 0.230)		
TV6 (Week 52) (N=94 LD - 110 HD)	-0.70 (± 0.239)	-0.88 (± 0.229)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

12-month period

Adverse event reporting additional description:

218 patients experienced at least 1 TEAE. There were 35 patients who experienced a serious TEAE, 26 patients who experienced a TEAE that led to study withdrawal, 30 patients that led to study drug discontinuation, 10 led to drug dose reduction, 31 experienced severe TEAE. No death occurred during this study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	CVT-301 Low Dose

Reporting group description:

Capsules of 60 mg of levodopa inhalational powder used up to 5 times/day for OFF episodes for 12 months duration.

Reporting group title	CVT-301 High Dose

Reporting group description:

Capsules of 84 mg of levodopa inhalational powder used up to 5 times/day for OFF episodes for 12 months duration.

Serious adverse events	CVT-301 Low Dose	CVT-301 High Dose	
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 153 (14.38%)	13 / 159 (8.18%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostrate cancer			
subjects affected / exposed	1 / 153 (0.65%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostrate cancer metastatic			
subjects affected / exposed	0 / 153 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Bone graft			

subjects affected / exposed	0 / 153 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 153 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 153 (0.65%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 153 (1.31%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	1 / 153 (0.65%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Impulse-control disorder			
subjects affected / exposed	0 / 153 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide threat			
subjects affected / exposed	0 / 153 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device connection tissue			

subjects affected / exposed	1 / 153 (0.65%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Hip fracture			
subjects affected / exposed	2 / 153 (1.31%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	1 / 153 (0.65%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	1 / 153 (0.65%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 153 (0.65%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	0 / 153 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 153 (0.65%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	1 / 153 (0.65%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Angina pectoris			
subjects affected / exposed	2 / 153 (1.31%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 153 (0.65%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mycocardial infarction			
subjects affected / exposed	0 / 153 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus node dysfunction			
subjects affected / exposed	1 / 153 (0.65%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Central nervous system lesion			
subjects affected / exposed	0 / 153 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic encephalaopathy			
subjects affected / exposed	1 / 153 (0.65%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parkinson's disease			
subjects affected / exposed	1 / 153 (0.65%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	1 / 153 (0.65%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Dysphagia			
subjects affected / exposed	1 / 153 (0.65%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 153 (0.65%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 153 (0.65%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 153 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 153 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Megacolon			
subjects affected / exposed	0 / 153 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 153 (0.65%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal achalasia			
subjects affected / exposed	1 / 153 (0.65%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			

subjects affected / exposed	0 / 153 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 153 (0.65%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 153 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	3 / 153 (1.96%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	1 / 153 (0.65%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc degeneration			
subjects affected / exposed	0 / 153 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoporotic fracture			
subjects affected / exposed	0 / 153 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal column stenosis			
subjects affected / exposed	0 / 153 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Clostridium difficile immunisation			
subjects affected / exposed	0 / 153 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis C			
subjects affected / exposed	1 / 153 (0.65%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising soft tissue infection			
subjects affected / exposed	1 / 153 (0.65%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneuomonia			
subjects affected / exposed	1 / 153 (0.65%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 153 (0.65%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 153 (0.65%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	CVT-301 Low Dose	CVT-301 High Dose	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	103 / 153 (67.32%)	115 / 159 (72.33%)	
Injury, poisoning and procedural complications			

Fall			
subjects affected / exposed	24 / 153 (15.69%)	17 / 159 (10.69%)	
occurrences (all)	26	22	
Nervous system disorders			
Dyskinesia			
subjects affected / exposed	6 / 153 (3.92%)	10 / 159 (6.29%)	
occurrences (all)	6	11	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	25 / 153 (16.34%)	23 / 159 (14.47%)	
occurrences (all)	28	27	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	8 / 153 (5.23%)	3 / 159 (1.89%)	
occurrences (all)	9	4	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	10 / 153 (6.54%)	12 / 159 (7.55%)	
occurrences (all)	10	13	
Nasopharyngitis			
subjects affected / exposed	8 / 153 (5.23%)	4 / 159 (2.52%)	
occurrences (all)	8	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 September 2014	In the USA, the original protocol CVT-301-004E Version 1.0 was submitted to the FDA on 25 August 2014 in Investigational New Drug application 115750, Sequence 0018; however, it was not activated and was never provided to any study sites. The protocol was subsequently amended to Version 1.1, which included minor administrative changes and clarifications that did not impact the study design or patient safety. Version 1.1 was provided to all study sites in the USA and Canada. The protocol was amended to Version 2.0 that also contained minor clarifications that did not impact the study design or patient safety and 3.0 was submitted to the FDA on 12 December 2014 in Investigational New Drug application 115750, Sequence 0024. It should be noted that Version 2.0 was never activated nor implemented at any study sites, and Version 3.0 was implemented only in Canada. Version 4.0 replaced Version 1.1 at all study sites in the USA; in Canada, Version 4.0 replaced Version 3.0. Version 4.0 was a major amendment that included, among other updates: • Removal of pulmonary assessments from the neurology sites to a dedicated pulmonary function facility after TV1. Removal of post-Screening UPDRS Part 3; simplified objectives to ensure consistency with study CVT-301-004. • Addition of 2 efficacy scales (PHQ-9 and Impact of Parkinson's OFF Episodes Patient Survey) for consistency with the core study, CVT-301-004. • Enrollment opened to patients from the observational arm of CVT-301-005 and from study CVT-301-009. • Enrollment closed to former patients from the CVT-301-003 study as patients may have developed tolerability for CVT-301. • Expanded the study to sites in Europe to align with the core study, CVT-301-004. Version 5.0 included the recommendations by the Agency to assess withdrawal and rebound including the Movement Disorder Society-UPDRS parts 1B and 2 during 28 days when completing withdrawal assessments at home.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported