Clinical trial results:
A Phase 3, Randomized Study Investigating the Safety of CVT-301 (Levodopa Inhalation Powder) in Parkinson's Disease Patients With Motor Response Fluctuations (OFF Phenomena) Compared to an Observational Cohort Control.

Summary

EudraCT number	2014-003799-22
Trial protocol	HU GB CZ DE ES BE AT
Global end of trial date	16 May 2017

Results information

Result version number	v1 (current)
This version publication date	29 April 2018
First version publication date	29 April 2018

Trial information

Trial identification

Sponsor protocol code	CVT-301-005

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02352363
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	Regulatory Affairs, INC Research, 44 127648 1000, SM_Regaffairs_eu_ap@increscarch.com
Scientific contact	Regulatory Affairs, INC Research, 44 127648 1000, SM_Regaffairs_eu_ap@increscarch.com
Sponsor organisation name	Acorda Therapeutics
Sponsor organisation address	420 Saw Mill River Road, Ardsley, United States, 10502
Public contact	Renee Rifelli, Acorda Therapeutics, 914 326-5827, rrifelli@acorda.com
Scientific contact	Renee Rifelli, Acorda Therapeutics, 914 326-5827, rrifelli@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	16 May 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 May 2017
Global end of trial reached?	Yes
Global end of trial date	16 May 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To characterize the 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 within the CVT 301 treated patients.

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	08 April 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: 93
Country: Number of subjects enrolled	Romania: 89
Country: Number of subjects enrolled	Spain: 36
Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	Austria: 12
Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	Czech Republic: 38
Country: Number of subjects enrolled	France: 20
Country: Number of subjects enrolled	Germany: 28

Country: Number of subjects enrolled	Hungary: 5
Country: Number of subjects enrolled	Israel: 21
Country: Number of subjects enrolled	Serbia: 15
Country: Number of subjects enrolled	United States: 27
Worldwide total number of subjects	398
EEA total number of subjects	335

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)	196
From 65 to 84 years	202
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients participated in the study from 8-April-2015 to 16-May-2017. Most patients were from Europe (93.2%). Largest population from Poland (23.4%) and Romania (22.4%). The remaining countries each contributed less than 10% of patients.

Pre-assignment

Screening details:

A total of 408 (79.5%) of the 513 patients screened were randomly assigned to CVT-301(n = 278) or the observational cohort (n = 130). Of these 408 patients, 398 received at least 1 dose of inhaled CVT-301 (CVT-301 treatment group) or came in for OV1 (observational cohort) and were included in the Safety Population.

Period 1

Period 1 title	12-month period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

This study was a 12-month, open-label, randomized, multicenter study that evaluated the safety and effects of inhaled CVT-301 84 mg for the treatment of up to 5 OFF periods per day in patients with PD experiencing motor fluctuations (OFF periods) and included a concurrent observational cohort of patients with PD managed using standard-of-care treatments.

Arms

Are arms mutually exclusive?	Yes
Arm title	CVT-301

Arm description:

CVT-301 is an investigational during and device combination that delivers levodopa to the lungs by oral inhalation via a breath-actuated inhaler.

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

Dosage and administration details:

Inhalation of two capsules up to 5 times daily.

Arm title	Observational Cohort

Arm description:

Patients who were randomly assigned to the observational cohort (CVT-301-naïve patients) and who completed all study visits per protocol without any safety issues were allowed to enroll in a long-term safety extension study (CVT-301-004E) if they met that study’s eligibility criteria.

Arm type	Observational

No investigational medicinal product assigned in this arm

Number of subjects in period 1	CVT-301	Observational Cohort
Started	271	127
Completed	204	106
Not completed	67	21
Consent withdrawn by subject	30	21
Adverse event, non-fatal	26	-
Lost to follow-up	2	-
Lack of efficacy	8	-
Protocol deviation	1	-

Baseline characteristics

Reporting groups

Reporting group title	12-month period

Reporting group description: -

Reporting group values	12-month period	Total	
Number of subjects	398	398	
Age categorical			
In the Safety Population, mean age was 63.8 years. Race was White for 390 patients (98.0%) and ethnicity was non-Hispanic for 391 patients (98.2%). There were 239 male patients (60.1%) and 159 female patients (39.9%).			
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)	196	196	
From 65-84 years	202	202	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	63.8		
full range (min-max)	37 to 80	-	
Gender categorical			
Units: Subjects			
Female	159	159	
Male	239	239	

Subject analysis sets

Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

A total of 408 (79.5%) of the 513 patients screened were randomly assigned to CVT-301 (n = 278) or the observational cohort (n = 130). Of these 408 patients, 398 received at least 1 dose of inhaled CVT-301 (CVT-301 treatment group) or came in for OV1 (observational cohort) and were included in the Safety Population.

Reporting group values	Safety Population		
Number of subjects	398		
Age categorical			
In the Safety Population, mean age was 63.8 years. Race was White for 390 patients (98.0%) and ethnicity was non-Hispanic for 391 patients (98.2%). There were 239 male patients (60.1%) and 159 female patients (39.9%).			
Units: Subjects			
In utero	0		

Preterm newborn infants (gestational age < 37 wks)	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)	196		
From 65-84 years	202		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean	63.8		
full range (min-max)	37 to 80		
Gender categorical			
Units: Subjects			
Female	159		
Male	239		

End points

End points reporting groups

Reporting group title	CVT-301

Reporting group description:

CVT-301 is an investigational during and device combination that delivers levodopa to the lungs by oral inhalation via a breath-actuated inhaler.

Reporting group title	Observational Cohort

Reporting group description:

Patients who were randomly assigned to the observational cohort (CVT-301-naïve patients) and who completed all study visits per protocol without any safety issues were allowed to enroll in a long-term safety extension study (CVT-301-004E) if they met that study's eligibility criteria.

Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

A total of 408 (79.5%) of the 513 patients screened were randomly assigned to CVT-301 (n = 278) or the observational cohort (n = 130). Of these 408 patients, 398 received at least 1 dose of inhaled CVT-301 (CVT-301 treatment group) or came in for OV1 (observational cohort) and were included in the Safety Population.

Primary: Pulmonary safety by FEV1

End point title	Pulmonary safety by FEV1[1]

End point description:

End point type	Primary

End point timeframe:

12 months

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 is an open labeled safety study evaluating the pulmonary safety assessed by spirometry. Formal statistical testing was not specified for the primary endpoint of pulmonary safety.

End point values	CVT-301	Observational Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	271	127		
Units: FEV1				
arithmetic mean (standard deviation)	2.665 (± 0.6977)	2.645 (± 0.8233)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 52 Week treatment period.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups	
Reporting group title	Observational Cohort
Reporting group description: -	
Reporting group title	CVT-301
Reporting group description: -	

Serious adverse events	Observational Cohort	CVT-301	
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 127 (10.24%)	42 / 271 (15.50%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign ovarian tumor			
subjects affected / exposed	0 / 127 (0.00%)	1 / 271 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	0 / 127 (0.00%)	1 / 271 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatic adenoma			
subjects affected / exposed	0 / 127 (0.00%)	1 / 271 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine cancer			

subjects affected / exposed	0 / 127 (0.00%)	1 / 271 (0.37%)	
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			
Asthenia			
subjects affected / exposed	1 / 127 (0.79%)	0 / 271 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gait disturbance			
subjects affected / exposed	1 / 127 (0.79%)	0 / 271 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 127 (0.79%)	0 / 271 (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			
Anoxia			
subjects affected / exposed	0 / 127 (0.00%)	1 / 271 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronhcial hyperreactivity			
subjects affected / exposed	0 / 127 (0.00%)	1 / 271 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pulmonary embolism			
subjects affected / exposed	0 / 127 (0.00%)	1 / 271 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 127 (0.00%)	1 / 271 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Restrictive pulmonary disease			
subjects affected / exposed	0 / 127 (0.00%)	1 / 271 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depressed mood			
subjects affected / exposed	0 / 127 (0.00%)	1 / 271 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dopamine dysregulation syndrome			
subjects affected / exposed	0 / 127 (0.00%)	1 / 271 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	0 / 127 (0.00%)	1 / 271 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood pressure increased			
subjects affected / exposed	0 / 127 (0.00%)	1 / 271 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	0 / 127 (0.00%)	2 / 271 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal wound dehiscence			
subjects affected / exposed	0 / 127 (0.00%)	1 / 271 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			

subjects affected / exposed	0 / 127 (0.00%)	1 / 271 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand fracture			
subjects affected / exposed	0 / 127 (0.00%)	1 / 271 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	1 / 127 (0.79%)	0 / 271 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 127 (0.00%)	1 / 271 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	0 / 127 (0.00%)	1 / 271 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	0 / 127 (0.00%)	1 / 271 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Rib fracture			
subjects affected / exposed	1 / 127 (0.79%)	0 / 271 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 127 (0.00%)	1 / 271 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			

subjects affected / exposed	0 / 127 (0.00%)	1 / 271 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 127 (0.79%)	1 / 271 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 127 (0.00%)	1 / 271 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Parkinson's disease			
subjects affected / exposed	2 / 127 (1.57%)	2 / 271 (0.74%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 127 (0.00%)	1 / 271 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyskinesia			
subjects affected / exposed	0 / 127 (0.00%)	1 / 271 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 127 (0.00%)	1 / 271 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	1 / 127 (0.79%)	0 / 271 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Occipital neuralgia			

subjects affected / exposed	0 / 127 (0.00%)	1 / 271 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 127 (0.00%)	1 / 271 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 127 (0.79%)	1 / 271 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 127 (1.57%)	0 / 271 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 127 (0.00%)	2 / 271 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 127 (0.00%)	1 / 271 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 127 (0.00%)	1 / 271 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 127 (0.00%)	1 / 271 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cholecystitis			
subjects affected / exposed	0 / 127 (0.00%)	1 / 271 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholethiasis			
subjects affected / exposed	0 / 127 (0.00%)	1 / 271 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	0 / 127 (0.00%)	1 / 271 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 127 (0.00%)	1 / 271 (0.37%)	
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	0 / 127 (0.00%)	3 / 271 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	0 / 127 (0.00%)	2 / 271 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	1 / 127 (0.79%)	1 / 271 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lunar spinal stenosis			

subjects affected / exposed	1 / 127 (0.79%)	0 / 271 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	0 / 127 (0.00%)	1 / 271 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spondylitis			
subjects affected / exposed	0 / 127 (0.00%)	1 / 271 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertebral formalin stenosis			
subjects affected / exposed	1 / 127 (0.79%)	0 / 271 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	0 / 127 (0.00%)	4 / 271 (1.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 127 (0.79%)	0 / 271 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 127 (0.79%)	0 / 271 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	0 / 127 (0.00%)	1 / 271 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	1 / 127 (0.79%)	0 / 271 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound			
subjects affected / exposed	0 / 127 (0.00%)	1 / 271 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 127 (0.00%)	1 / 271 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 127 (0.00%)	1 / 271 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 127 (0.00%)	2 / 271 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 127 (0.00%)	1 / 271 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0.03 %

Non-serious adverse events	Observational Cohort	CVT-301	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	73 / 127 (57.48%)	192 / 271 (70.85%)	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	7 / 127 (5.51%)	22 / 271 (8.12%)	
occurrences (all)	8	28	

Vascular disorders Hypertension subjects affected / exposed occurrences (all)	4 / 127 (3.15%) 4	9 / 271 (3.32%) 9	
Nervous system disorders Dyskinesia subjects affected / exposed occurrences (all) Parkinson's disease subjects affected / exposed occurrences (all)	5 / 127 (3.94%) 5 4 / 127 (3.15%) 4	17 / 271 (6.27%) 18 8 / 271 (2.95%) 8	
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	0 / 127 (0.00%) 0	10 / 271 (3.69%) 12	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Sputum discoloured subjects affected / exposed occurrences (all) Throat Irritation subjects affected / exposed occurrences (all)	0 / 127 (0.00%) 0 0 / 127 (0.00%) 0 0 / 127 (0.00%) 0	36 / 271 (13.28%) 43 9 / 271 (3.32%) 11 9 / 271 (3.32%) 10	
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	5 / 127 (3.94%) 5	0 / 271 (0.00%) 0	
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) Arthralgia subjects affected / exposed occurrences (all) Musculoskeletal pain	4 / 127 (3.15%) 4 0 / 127 (0.00%) 0	12 / 271 (4.43%) 19 8 / 271 (2.95%) 8	

subjects affected / exposed	4 / 127 (3.15%)	0 / 271 (0.00%)	
occurrences (all)	4	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	7 / 127 (5.51%)	18 / 271 (6.64%)	
occurrences (all)	8	20	
Upper respiratory tract infection			
subjects affected / exposed	0 / 127 (0.00%)	13 / 271 (4.80%)	
occurrences (all)	0	16	
Bronchitis			
subjects affected / exposed	4 / 127 (3.15%)	0 / 271 (0.00%)	
occurrences (all)	6	0	
Influenza			
subjects affected / exposed	4 / 127 (3.15%)	0 / 271 (0.00%)	
occurrences (all)	4	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 September 2015	Protocol CVT-301-005, Version 1.0 was never activated nor implemented at any study sites in the US or outside of the US except for Spain and the UK. Protocol CVT-301-005, Version 2.0 was submitted to the US Food and Drug Administration (FDA) and to Health Authorities outside of the US and was implemented at all study sites. Protocol Version 2.0 incorporated changes that clarified spirometry inclusion criteria, excluded patients treated with an investigational drug within 4 weeks or 5 half-lives before Screening, and removed the requirement that the onset time of dyskinesia be recorded during the 60-minute post-dose period. Protocol Version 2.1 reflected the local regulatory requirements in Belgium and Germany to include more stringent pregnancy contraception inclusion criteria and to require at-home monthly pregnancy tests for women of childbearing age in the CVT-301 treatment group. Protocol CVT-301-005, Version 3.0 was submitted to the US FDA and to Health Authorities outside of the US and was implemented at all study sites. Protocol Version 3.0 and Version 3.1 incorporated changes to allow an unscheduled visit to occur between SV1 and SV2 for the purpose of repeating concordance testing, the reordering of secondary and exploratory endpoints, and administrative clarifications. Additional changes, including those made to the inclusion and exclusion criteria, are documented in the summary of changes in Protocol CVT-301-005, Version 4.0 was submitted to the US FDA but not to Health Authorities outside of the US and was not implemented at any study sites because enrollment of additional patients was deemed unnecessary. A summary of the protocols and protocol amendments that were implemented at sites in the US, 11 countries in Europe (Austria, Belgium, Czech Republic, France, Germany, Hungary, Poland, Romania, Serbia, Spain, and the UK), and Israel. Only the protocols and protocol amendments (including summaries of changes between protocol versions that were

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported