Clinical trial results:
A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Investigating the Efficacy and Safety of CVT-301 (Levodopa Inhalation Powder) in Parkinson?s Disease Patients With Motor Response Fluctuations (OFF Phenomena) (SPAN-PD?)

Summary

EudraCT number	2015-005067-17
Trial protocol	CZ ES
Global end of trial date	06 December 2016

Results information

Result version number	v1 (current)
This version publication date	28 February 2018
First version publication date	28 February 2018

Trial information

Trial identification

Sponsor protocol code	CVT-301-004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02240030
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 1276481000, SM_Regaffairs_eu_ap@increscarch.com
Scientific contact	Regulatory Affairs, INC Research, 44 1276481000, 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	Acorda Therapeutics, Acorda Therapeutics, 914 326-5827, rrifelli@acorda.com
Scientific contact	Acorda Therapeutics, 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	06 December 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 December 2016
Global end of trial reached?	Yes
Global end of trial date	06 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the effects of CVT-301 versus placebo on the change from pre-dose in Unified Parkinson?s Disease Rating Scale (UPDRS) Part 3 motor score at 30 minutes following treatment of patients experiencing an OFF episode at Treatment Visit 4 (TV4) (Week 12).

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	03 November 2014
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: 66
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	United States: 248
Country: Number of subjects enrolled	Canada: 20
Worldwide total number of subjects	339
EEA total number of subjects	71

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)	167
From 65 to 84 years	172
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were screened at 70 sites in the United States (US), Canada, and Europe. From this total, 65 sites enrolled patients in the study: 52 sites in the US, 4 sites in Canada, 8 sites in Poland, and 1 site in Spain.

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 week (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Subject, Data analyst, Carer, Assessor

Arms

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

Arm description:

Capsules of levodopa inhalational powder used up to 5 times/day for OFF episodes for 3 months duration

CVT-301

Arm type	Experimental
Investigational medicinal product name	Levodopa
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	CVT-301 Low Dose

Arm description:

Capsules of levodopa inhalational powder used up to 5 times/day for OFF episodes for 3 months duration

Arm type	Experimental
Investigational medicinal product name	CVT-301 Low Dose
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	Placebo

Arm description:

Capsules of inhalation-grade lactose used up to 5 times/day for OFF episodes for 3 months duration.

Arm type	Placebo
Investigational medicinal product name	Placebo
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.

Number of subjects in period 1	CVT-301 High Dose	CVT-301 Low Dose	Placebo
Started	114	113	112
Completed	97	96	97
Not completed	17	17	15
Consent withdrawn by subject	9	9	10
Adverse event, non-fatal	6	3	3
Other	1	2	2
Lost to follow-up	-	2	-
Lack of efficacy	1	1	-

Baseline characteristics

Reporting groups	
Reporting group title	CVT-301 High Dose
Reporting group description:	
Capsules of levodopa inhalational powder used up to 5 times/day for OFF episodes for 3 months duration CVT-301	

Reporting group title	CVT-301 Low Dose
Reporting group description:	
Capsules of levodopa inhalational powder used up to 5 times/day for OFF episodes for 3 months duration	

Reporting group title	Placebo
Reporting group description:	
Capsules of inhalation-grade lactose used up to 5 times/day for OFF episodes for 3 months duration.	

Reporting group values	CVT-301 High Dose	CVT-301 Low Dose	Placebo
Number of subjects	114	113	112
Age categorical			
Participants 339			
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)	58	54	55
From 65-84 years	56	59	57
85 years and over	0	0	0
Age continuous			
Idiopathic, PD aged 30-85			
Units: years			
log mean	63.5	63.9	62.6
standard deviation	± 7.97	± 9.24	± 8.83
Gender categorical			
Female and Male			
Units: Subjects			
Female	31	33	26
Male	83	80	86

Reporting group values	Total		
Number of subjects	339		
Age categorical			
Participants 339			
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)	167		
From 65-84 years	172		
85 years and over	0		
Age continuous			
Idiopathic, PD aged 30-85			
Units: years			
log mean			
standard deviation	-		
Gender categorical			
Female and Male			
Units: Subjects			
Female	90		
Male	249		

End points

End points reporting groups

Reporting group title	CVT-301 High Dose

Reporting group description:

Capsules of levodopa inhalational powder used up to 5 times/day for OFF episodes for 3 months duration

CVT-301

Reporting group title	CVT-301 Low Dose

Reporting group description:

Capsules of levodopa inhalational powder used up to 5 times/day for OFF episodes for 3 months duration

Reporting group title	Placebo

Reporting group description:

Capsules of inhalation-grade lactose used up to 5 times/day for OFF episodes for 3 months duration.

Primary: Unified Parkinson’s Disease Rating Scale (UPDRS) Part III

End point title	Unified Parkinson’s Disease Rating Scale (UPDRS) Part III

End point description:

Primary Efficacy Analysis: Change from Predose in the UPDRS Part 3 Score at 30 Minutes Postdose at Treatment Visit 4 for CVT-301 DL2
versus Placebo (ITT Population)

End point type	Primary

End point timeframe:

at week 12

End point values	CVT-301 High Dose	CVT-301 Low Dose	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	114	113	112	
Units: Units on Scale				
least squares mean (standard deviation)	-9.83 (± 1.506)	0 (± 0)	-5.91 (± 1.500)	

Statistical analyses

Statistical analysis title	Primary Efficacy Endpoint

Statistical analysis description:

The statistical hypothesis to be tested for the primary efficacy variable was the following:
H0: μa = μp versus Ha: μa ≠ μp
μ = mean change from predose in UPDRS Part 3 score at 30 minutes postdose
a = active treatment group (CVT-301 DL2, CVT-301 DL1)
p = placebo treatment group

Comparison groups	Placebo v CVT-301 High Dose
Number of subjects included in analysis	226
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Mixed models analysis

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:

Examiner-assessed observation - Subject Achieving Resolution of an OFF to and ON state within 60 Minutes at TV4 - Observed

End point type	Secondary

End point timeframe:

12-Weeks

End point values	CVT-301 High Dose	CVT-301 Low Dose	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	114	113	112	
Units: Participants				
number (not applicable)	56	55	35	

Statistical analyses

No statistical analyses for this end point

Secondary: UPDRS Part III motor score at 20 minutes

End point title	UPDRS Part III motor score at 20 minutes

End point description:

Change in UPDRS Part III (motor) score at 20 minutes from pre to post -dose with CVT-301 vs placebo at week 12

End point type	Secondary

End point timeframe:

12-Weeks

End point values	CVT-301 High Dose	CVT-301 Low Dose	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	95	97	95	
Units: Dispersion/Precision				
least squares mean (confidence interval 97.5%)	-9.04 (-11.70 to -6.37)	-8.47 (-11.11 to -5.82)	-6.49 (-9.15 to -3.83)	

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects who improved PGIC with CVT-301 vs. Placebo at week 12

End point title	Proportion of subjects who improved PGIC with CVT-301 vs. Placebo at week 12

End point description:

Patient Global impression of change at treatment visit 4 by improvement category

End point type	Secondary

End point timeframe:

12-Weeks

End point values	CVT-301 High Dose	CVT-301 Low Dose	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	98	99	97	
Units: Participants	70	61	45	

Statistical analyses

No statistical analyses for this end point

Secondary: UPDRS Part III at 10 min.

End point title	UPDRS Part III at 10 min.

End point description:

Change in UPDRS Part III (motor) score at 10 min from pre- to post-dose with CVT-301 vs Placebo at week 12

End point type	Secondary

End point timeframe:

12-Weeks

End point values	CVT-301 High Dose	CVT-301 Low Dose	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	95	97	95	
Units: Dispersion/Precision				
least squares mean (confidence interval 95%)	-6.45 (-8.62 to -4.27)	-5.16 (-7.31 to -3.00)	-4.18 (-6.35 to -2.01)	

Statistical analyses

No statistical analyses for this end point

Secondary: PD Patient Diary

End point title	PD Patient Diary

End point description:

Change from baseline in total daily OFF times for consecutive days prior to week 12 visit

End point type	Secondary

End point timeframe:

post week 12

End point values	CVT-301 High Dose	CVT-301 Low Dose	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	95	96	97	
Units: Dispersion/Precision				
least squares mean (confidence interval 95%)	-0.47 (-1.02 to 0.09)	-0.58 (-1.13 to -0.03)	-0.48 (-1.03 to 0.08)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

12 Week Study

Adverse event reporting additional description:

Of 339 patients, 179 (52.8%) experienced at least 1 TEAE during the study: 49 patients (43.8%) reported at least 1 TEAE while on placebo and 64 (56.6%) and 66 (57.9%) patients reported at least 1 TEAE while on CVT-301 DL1 and CVT-301 DL2, respectively.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10.0

Reporting groups

Reporting group title	CVT-301 High Dose

Reporting group description:

Capsules of levodopa inhalational powder used up to 5 times/day for OFF episodes for 3 months duration

Reporting group title	CVT-301 Low Dose

Reporting group description:

Capsules of levodopa inhalational powder used up to 5 times/day for OFF episodes for 3 months duration

Reporting group title	Placebo

Reporting group description:

Capsules of inhalation-grade lactose used up to 5 times/day for OFF episodes for 3 months duration.

Serious adverse events	CVT-301 High Dose	CVT-301 Low Dose	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 114 (1.75%)	6 / 113 (5.31%)	3 / 112 (2.68%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events			
Cardiac disorders			
Chest Pains	Additional description: Two subjects reported chest pain in the 60-mg group.		
subjects affected / exposed	0 / 114 (0.00%)	2 / 113 (1.77%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	0 / 114 (0.00%)	1 / 113 (0.88%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			

subjects affected / exposed	1 / 114 (0.88%)	1 / 113 (0.88%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	0 / 114 (0.00%)	1 / 113 (0.88%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	0 / 114 (0.00%)	0 / 113 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 114 (0.00%)	1 / 113 (0.88%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Pancreatitis acute			
subjects affected / exposed	0 / 114 (0.00%)	0 / 113 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Lumbar spinal stenosis			
subjects affected / exposed	1 / 114 (0.88%)	0 / 113 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 4 %

Non-serious adverse events	CVT-301 High Dose	CVT-301 Low Dose	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	66 / 114 (57.89%)	64 / 113 (56.64%)	49 / 112 (43.75%)
Injury, poisoning and procedural complications			

Fall			
subjects affected / exposed	3 / 114 (2.63%)	5 / 113 (4.42%)	2 / 112 (1.79%)
occurrences (all)	3	5	2
Nervous system disorders			
Dyskinesia			
subjects affected / exposed	4 / 114 (3.51%)	5 / 113 (4.42%)	0 / 112 (0.00%)
occurrences (all)	4	5	0
Dizziness			
subjects affected / exposed	1 / 114 (0.88%)	2 / 113 (1.77%)	5 / 112 (4.46%)
occurrences (all)	1	2	5
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	6 / 114 (5.26%)	0 / 113 (0.00%)	3 / 112 (2.68%)
occurrences (all)	6	0	4
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	17 / 114 (14.91%)	17 / 113 (15.04%)	2 / 112 (1.79%)
occurrences (all)	18	20	2
Throat Irritation			
subjects affected / exposed	1 / 114 (0.88%)	8 / 113 (7.08%)	0 / 112 (0.00%)
occurrences (all)	1	8	0
Sputum discoloured			
subjects affected / exposed	6 / 114 (5.26%)	0 / 113 (0.00%)	0 / 112 (0.00%)
occurrences (all)	6	0	0
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	7 / 114 (6.14%)	2 / 113 (1.77%)	3 / 112 (2.68%)
occurrences (all)	7	2	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 July 2015	Protocol Versions 2.0 and 3.0 (dated 22 October 2014 and 26 November 2014, respectively) were not implemented at the sites because of administrative oversight. Protocol Version 4.0, dated 10 July 2015, incorporated recommendations in the US Food and Drug Administration (FDA) Type B End-of-Phase 2 Meeting Minutes dated 07 Aug 2014 to reduce the number of secondary outcome measures in the hierarchy and reorder the objectives according to clinical relevance, taking statistical power into account.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

N/A

Notes: