



Clinical trial results:

A Phase 2b, Randomized, Double-blind, Placebo-controlled Study Investigating the Efficacy and Safety of Inhaled CVT-301 (Levodopa Inhalation Powder) in Parkinson's Disease Patients With Motor Response Fluctuations (OFF Phenomena).

Summary

EudraCT number	2012-005822-31
Trial protocol	GB IT
Global end of trial date	21 January 2014

Results information

Result version number	v1 (current)
This version publication date	06 June 2016
First version publication date	14 August 2015

Trial information

Trial identification

Sponsor protocol code	CVT-301-003
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01777555
WHO universal trial number (UTN)	-
Other trial identifiers	Sample data: Sample data

Notes:

Sponsors

Sponsor organisation name	Civitas Therapeutics, Inc., a wholly owned subsidiary of Acorda Therapeutics, Inc.
Sponsor organisation address	420 Saw Mill River Road, Ardsley, United States, 10502
Public contact	Acorda Medical Lead/Scientific Lead, Clinical Development & Medical Affairs (CDMA), +1 914-347-4300,
Scientific contact	Acorda Medical Lead/Scientific Lead, CDMA, +1 914-347-4300,

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	18 July 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	21 January 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial is to compare the effects of CVT-301 Dose Level 2 (DL2; high dose) and placebo on the mean change from pre-dose in average UPDRS Part 3 motor score at 10 to 60 minutes following treatment of patients experiencing an OFF episode at the end-of-treatment (EOT) visit (Visit 6).

Protection of trial subjects:

n/a

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 April 2013
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	Italy: 10
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	United States: 64
Country: Number of subjects enrolled	Serbia: 8
Worldwide total number of subjects	86
EEA total number of subjects	14

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)	49
From 65 to 84 years	37

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	89 ^[1]
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Number of subjects completed	86
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Pre-assignment subject non-completion reasons

Reason: Number of subjects	Withdrawn from study before receiving study drug: 3
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Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The number of patients (89) were randomized. (3) patients were withdrawn from study before receiving any study drug. (86) patients continued to Treatment Period 1.

Period 1

Period 1 title	Treatment Period
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Is this the baseline period?	Yes
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Allocation method	Randomised - controlled
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Blinding used	Double blind
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Roles blinded	Subject, Investigator, Carer, Assessor
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Arms

Are arms mutually exclusive?	Yes
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Arm title	Placebo
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Arm description: -

Arm type	Placebo
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Investigational medicinal product name	Placebo
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Investigational medicinal product code	
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Other name	
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Pharmaceutical forms	Capsule, hard
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Routes of administration	Inhalation use
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Dosage and administration details:

Placebo powder was intended to provide a sensation of dose administration, but was not intended to provide a respirable dose.

Arm title	CVT-301
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Arm description: -

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

CVT-301 capsule designed to deliver an approximate respirable dose.

Number of subjects in period 1	Placebo	CVT-301
Started	43	43
Completed	43	43

Period 2

Period 2 title	Follow-up Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo
Arm description: -	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Inhalation use

Dosage and administration details:

Placebo consists of inhalation grade lactose monohydrate 120MS, United States Pharmacopeia (USP).

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

Dosage and administration details:

CVT-301 capsule designed to deliver an approximate respirable dose.

Number of subjects in period 2	Placebo	CVT-301
Started	43	43
Completed	36	39
Not completed	7	4
Consent withdrawn by subject	3	3

Adverse event, non-fatal	3	1
Lost to follow-up	1	-

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description: -	
Reporting group title	CVT-301
Reporting group description: -	

Reporting group values	Placebo	CVT-301	Total
Number of subjects	43	43	86
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	62.7	62	
standard deviation	± 9.08	± 8.36	-
Gender categorical Units: Subjects			
Female	11	18	29
Male	32	25	57

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: -	
Reporting group title	CVT-301
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	CVT-301
Reporting group description: -	
Subject analysis set title	ITT Population
Subject analysis set type	Intention-to-treat
Subject analysis set description: The Intent-to-Treat (ITT) population will include all patients who received at least one dose of inhaled CVT-301 or placebo. Patients will be analyzed according to randomized treatment. The ITT Population will be used for all analyses of efficacy endpoints and summaries of patient demographic and baseline characteristics.	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description: The Safety Population will include all patients who received at least one dose of inhaled CVT-301 or placebo. Patients will be analyzed according to treatment received. The Safety Population will be used for all analyses of safety endpoints.	

Primary: UPDRS Part 3 Score Mean Change From Predose to 10 to 60 Minutes Postdose at Visit 6

End point title	UPDRS Part 3 Score Mean Change From Predose to 10 to 60 Minutes Postdose at Visit 6
End point description:	
End point type	Primary
End point timeframe: Predose to 10 to 60 Minutes Postdose	

End point values	Placebo	CVT-301		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	42		
Units: Units on a scale				
least squares mean (standard error)	-3.07 (\pm 1.54)	-10.02 (\pm 1.5)		

Statistical analyses

Statistical analysis title	UPDRS Part 3 Score Mean Change at Visit 6
Statistical analysis description: MMRM model uses UPDRS Part III total score at 10 to 60 minutes at visits 4, 5, and 6 as the dependent variable, and includes baseline PD severity, country, treatment, visit, and treatment-by-visit interaction	

as factors and baseline UPDRS Part III score, screening score in OFF state, as a covariate.

Comparison groups	Placebo v CVT-301
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	other ^[1]
P-value	< 0.001 ^[2]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-6.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.31
upper limit	-3.6
Variability estimate	Standard error of the mean
Dispersion value	1.5

Notes:

[1] - Mixed effect Model Repeat Measurement

[2] - CVT-301 p-value at Visit 6

Dispersion value SE of the mean shown below is for CVT-301. Placebo (SE) dispersion value is 1.544

Secondary: Change from pre-dose in the average UPDRS Part 3 motor score at the end of 1 week of treatment (Visit 4)

End point title	Change from pre-dose in the average UPDRS Part 3 motor score at the end of 1 week of treatment (Visit 4)
End point description:	
ITT Population	
End point type	Secondary
End point timeframe:	
10 to 60 minutes post-dose	

End point values	Placebo	CVT-301		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	42		
Units: Units on a scale				
least squares mean (standard error)	-5.3 (± 1.53)	-9.9 (± 1.49)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients achieving objective UPDRS 3 motor response (≥30%)

End point title	Number of patients achieving objective UPDRS 3 motor response (≥30%)
End point description:	
ITT Population	
Objective motor response is defined as a patient having ≥30% reduction in the UPDRS Part 3 total score	

from pre-dose to post-dose at any time point post-dose.

End point type	Secondary
End point timeframe:	
From 10 to 60 minutes post-dose visits 4, 5 and 6.	

End point values	Placebo	CVT-301		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	43		
Units: Number				
Visit 4 (N=40/42) \geq 30% reduction	15	27		
Visit 5 (N=39/40) \geq 30% reduction	11	28		
Visit 6 (N=36/38) \geq 30% reduction	10	27		

Statistical analyses

No statistical analyses for this end point

Secondary: Change and percent change in UPDRS Part 3 Total Score at specified time points from Pre-dose to Post-dose

End point title	Change and percent change in UPDRS Part 3 Total Score at specified time points from Pre-dose to Post-dose
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End point description:

End point type	Secondary
End point timeframe:	
10 to 60 minutes following treatment.	

End point values	Placebo	CVT-301		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	43		
Units: Percent change/Score				
arithmetic mean (standard deviation)				
Visit 4 Change 10 min post-dose (N=40/42)	-3.2 (\pm 6.59)	-6.1 (\pm 7.96)		
Visit 4 Percent Change 10 min post-dose (N=40/42)	-9.74 (\pm 17.86)	-15.18 (\pm 30.27)		
Visit 4 Change 20 min post-dose (N=40/42)	-5.9 (\pm 7.83)	-10 (\pm 9.32)		
Visit 4 Percent Change 20 min post-dose (N=40/42)	-18.25 (\pm 22)	-27.79 (\pm 33.95)		
Visit 4 Change 30 min post-dose (N=40/42)	-6.1 (\pm 7.71)	-11 (\pm 9.2)		
Visit 4 Percent Change 30 min post-dose (N=40/42)	-19.25 (\pm 25.14)	-31.83 (\pm 28.45)		
Visit 4 Change 60 min post-dose (N=40/42)	-4.2 (\pm 6.51)	-9.3 (\pm 11.12)		

Visit 4 Percent Change 60 min post-dose (N=40/42)	-13.73 (± 23.49)	-24.22 (± 40.68)		
Visit 5 Change 10 min Post-dose (N=38/40)	-2.5 (± 7.81)	-4.6 (± 7.11)		
Visit 5 Percent Change 10 min Post-dose (N=38/40)	-3.72 (± 25.02)	-13.96 (± 20.87)		
Visit 5 Change 20 min Post-dose (N=39/40)	-4.5 (± 7.53)	-9.8 (± 9.06)		
Visit 5 Percent Change 20 min Post-dose (N=39/40)	-9.71 (± 27.56)	-28.66 (± 25.7)		
Visit 5 Change 30 min Post-dose (N=39/40)	-3.4 (± 8.27)	-11.7 (± 10.8)		
Visit 5 Percent Change 30 min Post-dose (N=39/40)	-5.66 (± 30.63)	-33.55 (± 26.47)		
Visit 5 Change 60 min Post-dose (N=39/40)	-1.9 (± 6.07)	-11.4 (± 11.98)		
Visit 5 Percent Change 60 min Post-dose (N=39/40)	-0.91 (± 31.86)	-33.02 (± 30.53)		
Visit 6 Change 10 min Post-dose (N=36/38)	-2 (± 7.48)	-4.9 (± 7.82)		
Visit 6 Percent Change 10 min Post-dose (N=36/38)	-3.46 (± 27.49)	-14.45 (± 20)		
Visit 6 Change 20 min Post-dose (N=36/38)	-3.8 (± 8.96)	-8.9 (± 9.78)		
Visit 6 Percent Change 20 min Post-dose (N=36/38)	-8.81 (± 28.54)	-27.73 (± 27.42)		
Visit 6 Change 30 min Post-dose (N=36/38)	-3.3 (± 7.56)	-11.6 (± 9.67)		
Visit 6 Percent Change 30 min Post-dose (N=36/38)	-7.66 (± 27.35)	-35.27 (± 27.56)		
Visit 6 Change 60 min Post-dose (N=36/38)	-1.6 (± 6.53)	-11.2 (± 9.83)		
Visit 6 Percent Change 60 min Post-dose (N=36/38)	-2.47 (± 25.88)	-33.82 (± 28.22)		

Statistical analyses

No statistical analyses for this end point

Secondary: Examiner-rated Time to Resolution of OFF Episodes to ON State

End point title	Examiner-rated Time to Resolution of OFF Episodes to ON State
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End point description:

Time to Resolution of OFF Episodes to ON State is calculated as (Time patient turns "ON" – Time of study drug administration). Measure type number = 25% Quantile
999 number = NE (not equatable)

End point type	Secondary
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End point timeframe:

Following observed treatment of patients experiencing an Off episode at each visit

End point values	Placebo	CVT-301		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	43		
Units: Minutes				
number (confidence interval 95%)				
Visit 4 (N=40/42)	22.5 (13 to 30)	16 (9 to 20)		
Visit 5 (N=39/39)	17 (8 to 38)	15 (9 to 20)		
Visit 6 (N=36/37)	13.5 (10 to 999)	10 (8 to 18)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time from Dosing to Dyskinesia Onset

End point title	Time from Dosing to Dyskinesia Onset
End point description:	
ITT Population	
End point type	Secondary
End point timeframe:	
Following study medication administration at each visit.	

End point values	Placebo	CVT-301		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	43		
Units: Minutes				
arithmetic mean (standard deviation)				
Visit 4 (N=4/5)	21 (± 9.9)	44.8 (± 16.98)		
Visit 5 (N=2/12)	14 (± 12.73)	43 (± 27.76)		
Visit 6 (N=2/10)	29 (± 33.94)	29.3 (± 11.17)		

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence and Severity of Dyskinesia Visit 4

End point title	Occurrence and Severity of Dyskinesia Visit 4
End point description:	
Dyskinesia in Parkinson's Disease (DPD)	
End point type	Secondary
End point timeframe:	
Following study medication at visit 4 (Week 2).	

End point values	Placebo	CVT-301		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	43		
Units: Number				
DPD Turned ON Post Inhaled Treatment	18	28		
DPD Among Patients Turned ON Post Treatment- Yes	4	5		
DPD Among Patients Turned ON Post Treatment- No	14	23		
Dyskinesia Among All Patients - Yes	4	5		
Dyskinesia Among All Patients - No	36	37		
Severity of Dyskinesia - Mild	1	4		
Severity of Dyskinesia - Moderate	2	1		
Severity of Dyskinesia - Severe	0	0		
Severity of Dyskinesia - Unknown	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence and Severity of Dyskinesia Visit 5

End point title	Occurrence and Severity of Dyskinesia Visit 5
End point description:	Dyskinesia in Parkinson's Disease (DPD)
End point type	Secondary
End point timeframe:	Following study medication at visit 5 (Week 3).

End point values	Placebo	CVT-301		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	43		
Units: Number				
Turned ON Post Inhaled Treatment	16	30		
DPD Among Patients Turned ON Post Treatment- Yes	1	12		
DPD Among Patients Turned ON Post Treatment- No	15	18		
Dyskinesia Among All Patients - Yes	2	12		
Dyskinesia Among All Patients - No	37	28		
Severity of Dyskinesia - Mild	1	12		
Severity of Dyskinesia - Moderate	1	0		
Severity of Dyskinesia - Severe	0	0		
Severity of Dyskinesia - Unknown	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence and Severity of Dyskinesia Visit 6

End point title Occurrence and Severity of Dyskinesia Visit 6

End point description:

Dyskinesia in Parkinson's Disease (DPD)

End point type Secondary

End point timeframe:

Following study medication at visit 6 (Week 5).

End point values	Placebo	CVT-301		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	43		
Units: Number				
Turned ON Post Inhaled Treatment	13	30		
DPD Among Patients Turned ON Post Treatment- Yes	2	12		
DPD Among Patients Turned ON Post Treatment- No	11	18		
Dyskinesia Among All Patients - Yes	2	12		
Dyskinesia Among All Patients - No	34	26		
Severity of Dyskinesia - Mild	2	9		
Severity of Dyskinesia - Moderate	0	2		
Severity of Dyskinesia - Severe	0	0		
Severity of Dyskinesia - Unknown	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients achieving objective UPDRS III motor response ($\geq 20\%$ reduction, ≥ 6 point and ≥ 11 point reduction)

End point title Number of patients achieving objective UPDRS III motor response ($\geq 20\%$ reduction, ≥ 6 point and ≥ 11 point reduction)

End point description:

ITT Population

Objective motor response is defined as a patient having $\geq 20\%$ reduction, ≥ 6 point and ≥ 11 point reduction in the UPDRS Part III total score from pre-dose to post-dose at any time point post-dose.

End point type	Secondary
End point timeframe:	
From 10 to 60 minutes post-dose visits 4, 5 and 6.	

End point values	Placebo	CVT-301		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	43		
Units: Number				
Visit 4 (N=40/42) \geq 20% reduction	21	31		
Visit 5 (N=39/40) \geq 20% reduction	14	31		
Visit 6 (N=36/38) \geq 20% reduction	13	31		
Visit 4 (N=40/42) \geq 6 point reduction	22	32		
Visit 5 (N=39/40) \geq 6 point reduction	17	32		
Visit 6 (N=36/38) \geq 6 point reduction	13	31		
Visit 4 (N=40/42) \geq 11 point reduction	11	24		
Visit 5 (N=39/40) \geq 11 point reduction	11	26		
Visit 6 (N=36/38) \geq 11 point reduction	10	25		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean time from study treatment to resolution of an OFF episode to an ON state during 2 week at-home period

End point title	Mean time from study treatment to resolution of an OFF episode to an ON state during 2 week at-home period
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End point description:

End point type	Secondary
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End point timeframe:

At-home treatment weeks 1-2.

End point values	Placebo	CVT-301		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	43		
Units: Minutes				
least squares mean (standard error)	59.3 (\pm 6.92)	48.9 (\pm 6.78)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean daily ON time without dyskinesia, ON time with dyskinesia (troublesome and non-troublesome), and OFF time from PD diaries

End point title | Mean daily ON time without dyskinesia, ON time with dyskinesia (troublesome and non-troublesome), and OFF time from PD diaries

End point description:

ITT Population

ON time with dyskinesia (troublesome and non-troublesome)

End point type | Secondary

End point timeframe:

At Screening period and Treatment Weeks 1, 2 and 4.

End point values	Placebo	CVT-301		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	43		
Units: Hours				
least squares mean (standard error)				
Week 1 ON time without dyskinesia	0.05 (± 0.42)	0.43 (± 0.42)		
Week 2 ON time without dyskinesia	0.38 (± 0.46)	0.7 (± 0.46)		
Week 4 ON time without dyskinesia	0.19 (± 0.48)	0.59 (± 0.47)		
Week 1 ON time with dyskinesia	0.54 (± 0.26)	0.3 (± 0.25)		
Week 2 ON time with dyskinesia	0.35 (± 0.22)	0.17 (± 0.22)		
Week 4 ON time with dyskinesia	0.4 (± 0.27)	0.7 (± 0.27)		
Week 1 OFF time	-0.72 (± 0.35)	-0.99 (± 0.35)		
Week 2 OFF time	-0.77 (± 0.37)	-1.06 (± 0.37)		
Week 4 OFF time	-0.77 (± 0.38)	-1.64 (± 0.37)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of treated OFF episodes that resolve to an ON state at pre-specified time intervals (minutes) after study treatment

End point title | Number of treated OFF episodes that resolve to an ON state at pre-specified time intervals (minutes) after study treatment

End point description:

Cumulative number indicates the total number of resolved episodes during the week in question.

End point type | Secondary

End point timeframe:

At Treatment Weeks 1, 2, 3 and 4

End point values	Placebo	CVT-301		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	43		
Units: Cumulative Number				
Week 1 (≤ 5 min)	10	41		
Week 1 (≤ 10 min)	53	75		
Week 1 (≤ 20 min)	176	195		
Week 1 (≤ 30 min)	258	271		
Week 1 (≤ 45 min)	323	338		
Week 1 (≤ 180 min)	495	497		
Week 2 (≤ 5 min)	20	23		
Week 2 (≤ 10 min)	35	72		
Week 2 (≤ 20 min)	145	170		
Week 2 (≤ 30 min)	215	238		
Week 2 (≤ 45 min)	274	307		
Week 2 (≤ 180 min)	474	444		
Week 3 (≤ 5 min)	23	15		
Week 3 (≤ 10 min)	70	52		
Week 3 (≤ 20 min)	168	170		
Week 3 (≤ 30 min)	240	232		
Week 3 (≤ 45 min)	354	302		
Week 3 (≤ 180 min)	499	428		
Week 4 (≤ 5 min)	29	21		
Week 4 (≤ 10 min)	78	62		
Week 4 (≤ 20 min)	129	170		
Week 4 (≤ 30 min)	188	253		
Week 4 (≤ 45 min)	256	316		
Week 4 (≤ 180 min)	456	440		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 10 weeks.

Adverse event reporting additional description:

Treatment Emergent Adverse Events (TEAEs)

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	15.1
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Reporting groups

Reporting group title	Placebo
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Reporting group description: -

Reporting group title	CVT-301
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Reporting group description: -

Serious adverse events	Placebo	CVT-301	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 43 (2.33%)	0 / 43 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Drop attacks			
subjects affected / exposed	1 / 43 (2.33%)	0 / 43 (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: 4 %

Non-serious adverse events	Placebo	CVT-301	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 43 (13.95%)	17 / 43 (39.53%)	
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 43 (4.65%)	3 / 43 (6.98%)	
occurrences (all)	4	3	
Headache			

subjects affected / exposed occurrences (all)	2 / 43 (4.65%) 3	2 / 43 (4.65%) 2	
General disorders and administration site conditions Oedema peripheral subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1	2 / 43 (4.65%) 2	
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0	3 / 43 (6.98%) 4	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Sputum discoloured subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1 0 / 43 (0.00%) 0	3 / 43 (6.98%) 4 2 / 43 (4.65%) 3	
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0	2 / 43 (4.65%) 2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported