Clinical trial results:
A multicenter, parallel-group, rater-blinded, randomized clinical study investigating the efficacy, safety, tolerability and pharmacokinetics of 2 dosing regimens of ND0612H, a solution of levodopa/carbidopa delivered via a pump system as a continuous subcutaneous infusion in subjects with advanced Parkinson's disease

Summary

EudraCT number	2015-005078-39
Trial protocol	DE AT IT
Global end of trial date	31 January 2017

Results information

Result version number	v1 (current)
This version publication date	16 April 2024
First version publication date	16 April 2024

Trial information

Trial identification

Sponsor protocol code	ND0612H-006

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02577523
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	NeuroDerm Ltd.
Sponsor organisation address	3 Pekeris Street, Rehovot, Israel, 7670212
Public contact	Eti Lavi, NeuroDerm Ltd., 972 89462729, eti@neuroderm.com
Scientific contact	Nelson Lopes, MD, NeuroDerm Ltd., 972 89462729, nelson@neuroderm.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	29 November 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 January 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the effect of continuous SC infusion of 2 dosing regimens of ND0612H on daily "OFF" time

Protection of trial subjects:

- Guidelines for Management of the Infusion Sites (i.e. location, rotation, cleaning, inspection).
- Named and trained study partner to help the trial subject with the study procedures.
- Health Care Professionals (a Home Nursing Service) to train and supervise both the subjects and study partners with study drug administration and handling of the infusion pump system throughout the outpatient period.
- Option to directly roll-over to an open-label, long-term, safety study ND0612H-012.

Background therapy:

- Stable anti-PD medications other than oral LD/DDI or entacapone to be continued without change throughout the study.
- Adjunct oral IR LD/ CD as rescue or additional therapy was allowed as needed.

Evidence for comparator: -

Actual start date of recruitment	29 December 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	Austria: 3
Country: Number of subjects enrolled	Italy: 10
Country: Number of subjects enrolled	Israel: 13
Country: Number of subjects enrolled	United States: 12
Worldwide total number of subjects	38
EEA total number of subjects	13

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)	19
From 65 to 84 years	19
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Eleven (11) sites screened, randomized and treated subjects in 4 countries. The first subject was enrolled on 29 Dec 2015.

Pre-assignment

Screening details:

A total of 49 subjects were screened in this study, of whom 11 (22.4%) failed screening. Reasons for screening failures were:
- Eligibility criteria not met (7 subjects, 14.3% of all screened subjects)
- Subject withdrew consent (1 subject, 2.0% of all screened subjects)
- Other (3 subjects, 6.1% of all screened subjects)

Period 1

Period 1 title	Study treatment (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Assessor[1]

Blinding implementation details:

The study was rater-blinded. The blinded rater responsible for assessing the motor state ("OFF", "ON" without dyskinesia, "ON" with dyskinesia [mild, moderate, severe]) as well as time to full "ON" on Days 1, 2, 3, and 28, remained blinded to the subjects' treatment. Subjects knew which treatment regimen they were assigned to, as did the unblinded staff responsible for administering the study treatments and for recording most assessment results.

Arms

Are arms mutually exclusive?	Yes
Arm title	ND0612 (Levodopa/Carbidopa solution) Dosing Regimen 1

Arm description:

Dosing Regimen 1 of ND0612 (Levodopa/Carbidopa solution) continuous SC infusion over 24 hours.

Arm type	Experimental
Investigational medicinal product name	ND0612 (Levodopa/Carbidopa solution)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

The total daily dose of levodopa/carbidopa 720/90 mg. Device: CRONO TWIN pump system.

Arm title	ND0612 (Levodopa/Carbidopa solution) Dosing Regimen 2

Arm description:

Dosing Regimen 2 of ND0612 (Levodopa/Carbidopa solution) continuous SC infusion over 14 hours. Infusion started at wake-up time supplemented with an oral IR LD/CD tablet.

Arm type	Experimental
Investigational medicinal product name	ND0612 (Levodopa/Carbidopa solution)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

The total daily dose levodopa/carbidopa from ND0612 538/67 mg. Morning dose of oral IR-LD/CD 150/15 mg. Device: CRONO TWIN pump system.

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: The study was rater-blinded (no such option to choose). The blinded rater responsible for assessing the motor state ("OFF", "ON" without dyskinesia, "ON" with dyskinesia [mild, moderate, severe]) as well as time to full "ON" on Days 1, 2, 3, and 28, remained blinded to the subjects' treatment. Subjects knew which treatment regimen they were assigned to, as did the unblinded staff responsible for administering the study treatments and for recording most assessment results.

Number of subjects in period 1	ND0612 (Levodopa/Carbidopa solution) Dosing Regimen 1	ND0612 (Levodopa/Carbidopa solution) Dosing Regimen 2
Started	19	19
Completed	16	17
Not completed	3	2
Consent withdrawn by subject	1	-
Adverse event, non-fatal	1	1
Lack of efficacy	1	1

Baseline characteristics

Reporting groups	
Reporting group title	ND0612 (Levodopa/Carbidopa solution) Dosing Regimen 1
Reporting group description:	
Dosing Regimen 1 of ND0612 (Levodopa/Carbidopa solution) continuous SC infusion over 24 hours.	
Reporting group title	ND0612 (Levodopa/Carbidopa solution) Dosing Regimen 2
Reporting group description:	
Dosing Regimen 2 of ND0612 (Levodopa/Carbidopa solution) continuous SC infusion over 14 hours. Infusion started at wake-up time supplemented with an oral IR LD/CD tablet.	

Reporting group values	ND0612 (Levodopa/Carbidopa solution) Dosing Regimen 1	ND0612 (Levodopa/Carbidopa solution) Dosing Regimen 2	Total
Number of subjects	19	19	38
Age categorical			
Units: Subjects			
Adults (18-64 years)	10	9	19
From 65-84 years	9	10	19
Age continuous			
Units: years			
arithmetic mean	63	64	
standard deviation	± 10.1	± 8.5	-
Gender categorical			
Units: Subjects			
Female	7	5	12
Male	12	14	26
Modified Hoehn and Yahr Scale			
A commonly used system for describing how the symptoms of Parkinson's disease progress. Stage 0: No signs of disease. Stage 1: Unilateral symptoms only. Stage 1.5: Unilateral and axial involvement. Stage 2: Bilateral symptoms. No impairment of balance. Stage 2.5: Mild bilateral disease with recovery on pull test. Stage 3: Balance impairment. Mild to moderate disease. Physically independent. Stage 4: Severe disability, but still able to walk or stand unassisted. Stage 5: Needing a wheelchair or bedridden unless assisted.			
Units: Subjects			
Stage 1	1	0	1
Stage 1.5	0	1	1
Stage 2	13	11	24
Stage 2.5	4	5	9
Stage 3	1	2	3
Time since Parkinson's disease diagnosis			
Units: Years			
arithmetic mean	10.7	12.2	
standard deviation	± 5.5	± 5	-
Time since motor fluctuations			
Units: Years			
arithmetic mean	5.7	5.5	
standard deviation	± 6.9	± 4.8	-
Time since dyskinesia onset			
Units: Years			
arithmetic mean	3.1	4.2	

standard deviation	± 2.7	± 3.4	-
Daily “OFF” time			
"OFF" state is a phase with no response to medication and significant motor symptoms. An assessment of motor state ("OFF", "ON" without dyskinesia, "ON" with dyskinesia (mild, moderate, severe)) was performed by the blinded rater during 8 hours (normalized to 16 hours of awake time).			
Units: Hours			
arithmetic mean	5.6	5.0	
standard deviation	± 2.1	± 2.4	-
Daily “Good ON” time			
"ON" without dyskinesia and "ON" with mild dyskinesia. An assessment of motor state ("OFF", "ON" without dyskinesia, "ON" with dyskinesia (mild, moderate, severe)) was performed by the blinded rater during 8 hours (normalized to 16 hours of awake time).			
Units: Hours			
arithmetic mean	9.2	8.5	
standard deviation	± 3.3	± 3.3	-
Daily time with troublesome dyskinesia			
Dyskinesia defined as moderate or severe in intensity. An assessment of motor state ("OFF", "ON" without dyskinesia, "ON" with dyskinesia (mild, moderate, severe)) was performed by the blinded rater during 8 hours (normalized to 16 hours of awake time).			
Units: Hours			
arithmetic mean	1.2	2.5	
standard deviation	± 2.8	± 3.7	-
UPDRS Part III (motor) score			
Unified Parkinson's Disease Rating Scale (UPDRS) is divided into four scales. Part III (questions 18-31) is done as a motor examination. The various items to be rated are scored using a 5-point system (i.e., 0 is normal and 4 indicates a severe abnormality, half point scores are allowed for Part III questions). The range of score values is from 0 to 132. Higher value indicate greater impairment.			
Units: Score			
arithmetic mean	37.4	37.3	
standard deviation	± 14.5	± 13.3	-
Levodopa dose			
Units: mg			
arithmetic mean	996	948	
standard deviation	± 552	± 305	-

End points

End points reporting groups

Reporting group title	ND0612 (Levodopa/Carbidopa solution) Dosing Regimen 1
Reporting group description:	
Dosing Regimen 1 of ND0612 (Levodopa/Carbidopa solution) continuous SC infusion over 24 hours.	
Reporting group title	ND0612 (Levodopa/Carbidopa solution) Dosing Regimen 2
Reporting group description:	
Dosing Regimen 2 of ND0612 (Levodopa/Carbidopa solution) continuous SC infusion over 14 hours. Infusion started at wake-up time supplemented with an oral IR LD/CD tablet.	

Primary: Change in Daily "OFF" Time

End point title	Change in Daily "OFF" Time[1]
End point description:	
Based on Parkinson's disease symptom assessment, "ON" time is when there is good response to medication and few symptoms. "OFF" time is when no there is no response to medication and significant motor symptoms. An "ON/OFF" Log was completed by a blinded rater starting before the first dose of LD/DDI and following the first dose at 30 min intervals for 8 hrs. The changes in "OFF" time as hours (normalized to 16 hrs of awake time) during the 8 hrs of data collection were estimated. Negative change from baseline for "OFF" time indicates improvement.	
End point type	Primary
End point timeframe:	
Baseline to Day 28	

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: The purpose of this study was to explore efficacy and safety of the 2 treatment regimens; no formal hypothesis testing was to be performed (descriptive statistics only).

End point values	ND0612 (Levodopa/Carbidopa solution) Dosing Regimen 1	ND0612 (Levodopa/Carbidopa solution) Dosing Regimen 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: Hours				
least squares mean (confidence interval 95%)	-2.8 (-4.6 to -0.9)	-1.3 (-3.1 to 0.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: The Percentage of Subjects With Full "ON" at Approximately 08:00 and Approximately 09:00, as Determined by the Subject

End point title	The Percentage of Subjects With Full "ON" at Approximately 08:00 and Approximately 09:00, as Determined by the Subject[2]

End point description:

Based on Parkinson's disease symptom assessment, “ON” time is when there is good response to medication and few symptoms. "OFF" time is when no there is no response to medication and significant motor symptoms. Subjects were asked to indicate when exactly in their opinion they had turned to full “ON” (i.e. an “ON” response comparable to the “ON” response to standard oral LD/DDI treatment). Higher percentage of subjects with full “ON” on Day 28 indicates improvement.

End point type	Secondary

End point timeframe:

Baseline to Day 28

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Analysis for Regimen 1 (24-hr infusion) only. Regimen 2 was not optimized for morning efficacy assessment (it required the arrival of a nurse in the morning to administer oral IR LD/CD and begin the infusion).

End point values	ND0612 (Levodopa/Carbidopa solution) Dosing Regimen 1			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: Participants				
Day 28: Full "ON" by 8:00	7			
Day 28: Full "ON" by 9:00	13			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Daily "Good ON" Time as Assessed by a Blinded Rater

End point title	Change in Daily "Good ON" Time as Assessed by a Blinded Rater

End point description:

Based on Parkinson's disease symptom assessment, “ON” time is when there is good response to medication and few symptoms. "OFF" time is when no there is no response to medication and significant motor symptoms. “Good ON” time means “ON” time without troublesome dyskinesia (involuntary muscle movement), defined as the sum of "ON" time without dyskinesia and “ON” time with non-troublesome dyskinesia. An “ON/OFF” Log was completed by a blinded rater starting before the first dose of LD/DDI and following the first dose at 30 min intervals for 8 hrs. Daily total scores were normalized to 16 hours of awake time. Positive change from baseline for “ON” time without dyskinesia and for “Good ON” time, and a negative change in “ON” time with moderate or severe (troublesome) dyskinesia indicates improvement.

End point type	Secondary

End point timeframe:

Baseline to Day 28

End point values	ND0612 (Levodopa/Carbidopa solution) Dosing Regimen 1	ND0612 (Levodopa/Carbidopa solution) Dosing Regimen 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: Hours				
least squares mean (confidence interval 95%)	3.7 (1.9 to 5.6)	2.8 (1.0 to 4.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Morning UPDRS Part III (Motor) Scores

End point title	Change in Morning UPDRS Part III (Motor) Scores

End point description:

The Unified Parkinson’s Disease Rating Scale (UPDRS) is an Investigator-used rating tool to follow the longitudinal course of Parkinson's disease. UPDRS part III (motor) score is calculated as the sum of the individual UPDRS items 18-31, each of which are measured on a 5-point scale (i.e., 0 is normal and 4 indicates a severe abnormality). UPDRS part III was done as a motor examination on Day 1 before the first dose of standard oral LD/DDI and at the same time on Day 28. The range of score values is from 0 to 132. Higher scores correlate with greater motor impairment.

End point type	Secondary

End point timeframe:

Baseline to Day 28

End point values	ND0612 (Levodopa/Carbidopa solution) Dosing Regimen 1	ND0612 (Levodopa/Carbidopa solution) Dosing Regimen 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: Score				
least squares mean (confidence interval 95%)	-19.1 (-25.6 to -12.5)	-10.7 (-16.8 to -4.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in UPDRS Part II (ADL) Scores

End point title	Change in UPDRS Part II (ADL) Scores

End point description:

The Unified Parkinson's disease rating scale (UPDRS) is an Investigator-used rating tool to follow the

longitudinal course of Parkinson's disease. The UPDRS Part II (activity of daily living) score was calculated as the sum of the individual UPDRS items 5-17. The Part II score is the sum of the answers to the 13 questions that comprise Part II, each of which are measured on a 5-point scale (i.e., 0 is normal and 4 indicates a severe abnormality). The range of score values is from 0 to 52. Higher scores correlate with greater impairments for daily activities.

End point type	Secondary

End point timeframe:

Baseline to Day 28

End point values	ND0612 (Levodopa/Carbidopa solution) Dosing Regimen 1	ND0612 (Levodopa/Carbidopa solution) Dosing Regimen 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: Score				
least squares mean (confidence interval 95%)	-2.9 (-5.4 to -0.5)	-1.9 (-4.2 to 0.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: CGI-Improvement (CGI-I) Score as Assessed by Investigator

End point title	CGI-Improvement (CGI-I) Score as Assessed by Investigator

End point description:

Global improvement was rated by the investigator or designee using Clinical Global Impression of Improvement (CGI-I). The CGI-I employs a 7-point scale with 1 being “very much improved” and 7 being “very much worse” for improvement rating.

End point type	Secondary

End point timeframe:

Baseline to Day 28

End point values	ND0612 (Levodopa/Carbidopa solution) Dosing Regimen 1	ND0612 (Levodopa/Carbidopa solution) Dosing Regimen 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	18		
Units: Participants				
Very much improved	5	2		
Much improved	6	7		
Minimally improved	3	4		
No change	1	5		

Minimally worse	1	0		
Much worse	0	0		
Very much worse	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in PDQ-39 Summary Index and the 8-dimension Scores

End point title	Change in PDQ-39 Summary Index and the 8-dimension Scores

End point description:

Subjects were requested to rate their quality of life using the Quality of Life in Parkinson's Disease (PDQ)-39, a 39-item, self-administered questionnaire with 8 discrete dimensions (mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication, and bodily discomfort). The PDQ-39 Summary Index is the sum of the dimension scores divided by the number of dimensions. The total score values range from 0 to 100%. Higher scores indicate a worse quality of life.

End point type	Secondary

End point timeframe:

Baseline to Day 27

End point values	ND0612 (Levodopa/Carbidopa solution) Dosing Regimen 1	ND0612 (Levodopa/Carbidopa solution) Dosing Regimen 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: Score				
least squares mean (confidence interval 95%)	-7.5 (-12.9 to -2.1)	-3.7 (-8.9 to 1.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in PDSS-2 Total Score

End point title	Change in PDSS-2 Total Score

End point description:

The quality of night sleep was rated by the subjects using the Parkinson's Disease Sleep Scale (PDSS)-2, which includes questions addressing 15 commonly reported symptoms associated with sleep disturbance in PD. Each question is assessed from 0 (Always) to 10 (Never). The total score values range from 0 to 150. Higher scores indicate a lower quality of sleep, i.e., a reduction in the score indicates an improvement in sleep quality.

End point type	Secondary

End point timeframe:

Baseline to Day 27

End point values	ND0612 (Levodopa/Carbidopa solution) Dosing Regimen 1	ND0612 (Levodopa/Carbidopa solution) Dosing Regimen 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: Score				
least squares mean (confidence interval 95%)	-4.1 (-8.0 to -0.2)	-0.8 (-4.4 to 2.9)		

Statistical analyses

No statistical analyses for this end point

Post-hoc: Percentage of Subjects Who Achieved at Least Certain Percent Reduction in Average Daily Normalized "OFF" Time

End point title	Percentage of Subjects Who Achieved at Least Certain Percent Reduction in Average Daily Normalized "OFF" Time[3]

End point description:

Determination of percentage of subjects who had a complete and 50% reduction in daily “OFF” time from baseline to Day 28 during 8 hours observations.

End point type	Post-hoc

End point timeframe:

Baseline to Day 28

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This was a post-hoc analysis for Regimen 1 (24-hr infusion) only.

End point values	ND0612 (Levodopa/Carbidopa solution) Dosing Regimen 1			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: Participants				
Subjects who Achieved 50% reduction in average dai	12			
Subjects who Achieved complete reduction in averag	8			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From Baseline to the end of treatment plus 28 days	
Adverse event reporting additional description:	
Treatment emergent adverse events are defined as all AEs that start on or after the start of first study drug administration	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups	
Reporting group title	ND0612 Regimen 1 - 24-hr Infusion
Reporting group description:	
Dosing Regimen 1 of ND0612 (Levodopa/Carbidopa solution) continuous SC infusion over 24 hours. ND0612 (Levodopa/Carbidopa solution) The total daily dose of levodopa/carbidopa 720/90 mg. Device: CRONO TWIN pump system.	
Reporting group title	ND0612 Regimen 2 - 14-hr Infusion
Reporting group description:	
Dosing Regimen 2 of ND0612 (Levodopa/Carbidopa solution) continuous SC infusion over 14 hours. Infusion started at wake-up time supplemented with an oral IR LD/CD tablet. ND0612 (Levodopa/Carbidopa solution) + morning oral IR-LD/CD. The total daily dose levodopa/carbidopa from ND0612 538/67 mg. Morning dose of oral IR-LD/CD 150/15 mg. Device: CRONO TWIN pump system.	

Serious adverse events	ND0612 Regimen 1 - 24-hr Infusion	ND0612 Regimen 2 - 14-hr Infusion	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 19 (10.53%)	2 / 19 (10.53%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Facial bones fracture			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Orthostatic hypotension			

subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (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			
Parkinson's disease	Additional description: Worsening		
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Panniculitis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Subcutaneous abscess			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	ND0612 Regimen 1 - 24-hr Infusion	ND0612 Regimen 2 - 14-hr Infusion	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 19 (78.95%)	14 / 19 (73.68%)	
Vascular disorders			
Orthostatic hypotension			
subjects affected / exposed	2 / 19 (10.53%)	0 / 19 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 19 (10.53%)	0 / 19 (0.00%)	
occurrences (all)	3	0	
Parkinson's disease	Additional description: Worsening		
subjects affected / exposed	1 / 19 (5.26%)	2 / 19 (10.53%)	
occurrences (all)	1	3	
General disorders and administration			

site conditions			
Infusion site bruising			
subjects affected / exposed	4 / 19 (21.05%)	3 / 19 (15.79%)	
occurrences (all)	4	3	
Infusion site oedema			
subjects affected / exposed	1 / 19 (5.26%)	1 / 19 (5.26%)	
occurrences (all)	1	1	
Infusion site erythema			
subjects affected / exposed	5 / 19 (26.32%)	2 / 19 (10.53%)	
occurrences (all)	6	2	
Infusion site haematoma			
subjects affected / exposed	3 / 19 (15.79%)	1 / 19 (5.26%)	
occurrences (all)	5	1	
Infusion site haemorrhage			
subjects affected / exposed	2 / 19 (10.53%)	3 / 19 (15.79%)	
occurrences (all)	2	3	
Infusion site nodule			
subjects affected / exposed	11 / 19 (57.89%)	7 / 19 (36.84%)	
occurrences (all)	14	7	
Infusion site pain			
subjects affected / exposed	1 / 19 (5.26%)	3 / 19 (15.79%)	
occurrences (all)	1	4	
Infusion site pruritus			
subjects affected / exposed	2 / 19 (10.53%)	0 / 19 (0.00%)	
occurrences (all)	2	0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 19 (0.00%)	2 / 19 (10.53%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 January 2016	- Window for changing of infusion set, infusion initiation and duration added. - ECG was added to the early termination visit. - The injection sites instructions were revised. - Cannabis was added to the list of prohibited medications. - The prerequisites for an early termination visit were defined more clearly. - Dosing Regimen Satisfaction Questionnaire was added on Day 28 or to the Early Termination Visit. - Clarification on the conditions for administration of rescue/additional medication and for up/down titration of study treatment. - Superfluous photographing was removed from assessment of injection sites.
14 April 2016	- Clarifications regarding standard oral treatment, treatment regimen, named study partner, handling of the pump and study drug, Home Nursing Service. - Malignancies and defined viral infections were included in list of exclusion criteria. - Guidelines for the management of the infusion sites was added. - Sample size information was updated to include the standard deviation for the estimated within group change in daily “OFF” time. - The timing of urine pregnancy tests was updated. - Visit windows were clarified for the Maintenance period. - Storage conditions for study drug at the subjects’ home were updated. - The investigator Adverse Event causality assessment was changed to a binary assessment of "Related" or "Unrelated". Clarifications about SUSAR and SAE notification and publishing of the study results. Additional guidance was included in the instructions on the assessment of local safety parameters.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/33164945