Clinical trial results:
Intrathecal administration (pattern 100/3) of expanded autologous adult bone marrow mesenchymal troncal cells in established chronic spinal cord injuries

Summary

EudraCT number	2014-005613-24
Trial protocol	ES
Global end of trial date	04 January 2018

Results information

Result version number	v1 (current)
This version publication date	11 June 2022
First version publication date	11 June 2022

Trial information

Trial identification

Sponsor protocol code	CME-LEM3

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Fundación Investigación Biomédica Hospital Universitario Puerta de Hierro
Sponsor organisation address	C/ Joaquín Rodrigo, 2 Majadahonda, Madrid, Spain, 28222
Public contact	SIte contact point, Fundación Investigación Biomédica Hospital Universitario Puerta de Hierro, +34 911917760,
Scientific contact	SIte contact point, Fundación Investigación Biomédica Hospital Universitario Puerta de Hierro, +34 911917760,

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	04 January 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 January 2018
Global end of trial reached?	Yes
Global end of trial date	04 January 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To analyze the potential clinical efficacy of intrathecal administration, in the subarachnoid space, of in vitro expanded autologous adult bone marrow mesenchymal troncal cells in the treatment of patients with established chronic spinal cord injury (LEM)

Protection of trial subjects:

Previous to NC1 preparation, a sample of peripheral blood was retrieved from each patient for genomic studies in order to rule out chromosomal abnormalities that could discourage cell expansion.

Background therapy:

From the start of treatment until the end of the trial (month 10 after the first MSC administration) patients performed physical therapy exercises.

Evidence for comparator: -

Actual start date of recruitment	18 May 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 11
Worldwide total number of subjects	11
EEA total number of subjects	11

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)	11

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The planned duration of the clinical trial was 24 months. The duration of the recruitment phase was 12 months, the duration of the treatment phase was 7 months, and the duration of the follow-up period after the first administration of MSC was 10 months.

Pre-assignment

Screening details:

After signing the Informed Consent Form, participants were tested to determine if they met all the inclusion criteria and none of the exclusion criteria.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not applicable. All the participants received the same treatment.

Arms

Arm title	Arm 1

Arm description:

Treatment arm

Arm type	Experimental
Investigational medicinal product name	NC1
Investigational medicinal product code	
Other name	PEI number 12–141 (by the Spanish Agency of Medicament and Health Products)
Pharmaceutical forms	Suspension for injection
Routes of administration	Intrathecal use

Dosage and administration details:

Subarachnoid administration, by lumbar puncture, of 3 doses of 100 x 10^6 autologous mesenchymal stromal cells (MSCs) obtained from bone marrow, expanded and supported in autologous plasma, with intervals of 3 months between each administration (month 1, 4 and 7) reaching a total administration of 300 x 10^6 mesenchymal stromal cells for each patient.

Number of subjects in period 1	Arm 1
Started	11
Completed	10
Not completed	1
Adverse event, non-fatal	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial (overall period)

Reporting group description: -

Reporting group values	Overall trial (overall period)	Total	
Number of subjects	11	11	
Age categorical			
Age ranged between 28 and 62 years (mean ± standard deviation [SD], 44.91 ± 10.17 years)			
Units: Subjects			
Adults (18-64 years)	11	11	
Gender categorical Units: Subjects			
Female	4	4	
Male	7	7	
American Spinal Injury Association Impairment Scale (ASIA) grade Units: Subjects			
ASIA A	3	3	
ASIA B	4	4	
ASIA C	3	3	
ASIA D	1	1	
Spinal cord injury (SCI) vertebral level Units: Subjects			
Cervical level	4	4	
Dorsal level	4	4	
Dorsolumbar level	3	3	

End points

End points reporting groups

Reporting group title	Arm 1
Reporting group description: Treatment arm	
Subject analysis set title	Before treatment
Subject analysis set type	Per protocol
Subject analysis set description: Baseline characteristics of the subjects	
Subject analysis set title	At 4 months follow-up
Subject analysis set type	Per protocol
Subject analysis set description: Characteristics of the subjects at 4 months follow-up	
Subject analysis set title	At 7 months follow-up
Subject analysis set type	Per protocol
Subject analysis set description: Characteristics of the subjects at 7 months follow-up	
Subject analysis set title	At 10 months follow-up
Subject analysis set type	Per protocol
Subject analysis set description: Characteristics of the subjects at 10 months follow-up	

Primary: Change in the score in ASIA scale

End point title	Change in the score in ASIA scale
End point description: ASIA scale was used for sensitivity and motor assessments. Efficacy was assessed by taking into account the variation in the scores in the different scales between the subject´s inclusion in the study and the scores obtained at the end of the follow-up period.	
End point type	Primary
End point timeframe: Between the subject´s inclusion in the study and the end of the follow-up (FU) period.	

End point values	Before treatment	At 4 months follow-up	At 7 months follow-up	At 10 months follow-up
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	9	9	9	9
Units: Score				
arithmetic mean (standard deviation)				
Total Score	181.56 (± 66.44)	204.22 (± 57.40)	213.22 (± 59.22)	216.56 (± 61.63)
Pin Prick Score	61.11 (± 30.56)	74.56 (± 26.82)	79.56 (± 27.85)	80.11 (± 28.41)
Light Touch Score	67.44 (± 24.00)	75.11 (± 19.19)	78.33 (± 19.66)	80.44 (± 21.80)
Motor Score	53.00 (± 17.90)	54.56 (± 18.20)	55.33 (± 17.75)	56.00 (± 18.41)

Statistical analyses

Statistical analysis title	Total Score: before treatment vs at 4 months FU
Comparison groups	At 4 months follow-up v Before treatment
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.012
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Total Score: before treatment vs at 7 months FU
Comparison groups	Before treatment v At 7 months follow-up
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.009
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Total Score: before treatment vs at 10 months FU
Comparison groups	Before treatment v At 10 months follow-up
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.021
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	PinPrick Score: before treatment vs at 4 months FU
Comparison groups	Before treatment v At 4 months follow-up
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.012
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	PinPrick Score: before treatment vs at 7 months FU

Comparison groups	Before treatment v At 7 months follow-up
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.011
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	PinPrick Score: before treatment vs 10 months FU
Comparison groups	Before treatment v At 10 months follow-up
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.018
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Light Touch Score: before treatment vs 4 months FU
Comparison groups	Before treatment v At 4 months follow-up
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.018
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Light Touch Score: before treatment vs 7 months FU
Comparison groups	Before treatment v At 7 months follow-up
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.009
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Light Touch Score: before treatment vs 10 month FU
Comparison groups	Before treatment v At 10 months follow-up
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.011
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Motor Score: before treatment vs at 4 months FU
Comparison groups	Before treatment v At 4 months follow-up
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.048
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Motor Score: before treatment vs at 7 months FU
Comparison groups	Before treatment v At 7 months follow-up
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.028
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Motor Score: before treatment vs at 10 months FU
Comparison groups	Before treatment v At 10 months follow-up
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.028
Method	Wilcoxon (Mann-Whitney)

Primary: Change in the score in IANR-SCIFRS scale

End point title	Change in the score in IANR-SCIFRS scale

End point description:

IANR-SCIFRS scale: the SCI Functional Rating Scale of the International Association of Neurorestoratology scale. This scale evaluates the global spinal cord function through nine sections, with a final section that only applies to men and assesses sexual function. Efficacy was assessed by taking into account the variation in the scores on the different scales between the subject´s inclusion in the study and the scores obtained at the end of the follow-up period.

End point type	Primary

End point timeframe:

Between the subject´s inclusion in the study and the end of the follow-up period.

End point values	Before treatment	At 4 months follow-up	At 7 months follow-up	At 10 months follow-up
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	9	9	9	9
Units: Score				
arithmetic mean (standard deviation)				
Global Score	27.36 (± 9.38)	32.10 (± 7.23)	34.90 (± 5.59)	36.20 (± 5.71)
Sexual Score (only males)	1.00 (± 0.82)	1.00 (± 0.82)	1.14 (± 0.69)	1.29 (± 0.76)
Sphincter Score	2.00 (± 1.87)	2.56 (± 1.74)	3.22 (± 1.86)	3.33 (± 1.94)

Statistical analyses

Statistical analysis title	Global Score: before treatment vs at 4 months FU
Comparison groups	Before treatment v At 4 months follow-up
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.012
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Global Score: before treatment vs at 7 months FU
Comparison groups	Before treatment v At 7 months follow-up
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.009
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Global Score: before treatment vs at 10 months FU
Comparison groups	Before treatment v At 10 months follow-up
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.009
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Sexual Score: before treatment vs at 4 months FU
Comparison groups	Before treatment v At 4 months follow-up

Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0 [1]
Method	Wilcoxon (Mann-Whitney)

Notes:

[1] - The p-value was non-computable

Statistical analysis title	Sexual Score: before treatment vs at 7 months FU
Comparison groups	Before treatment v At 7 months follow-up
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.317
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Sexual Score: before treatment vs at 10 months FU
Comparison groups	Before treatment v At 10 months follow-up
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.157
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Sphincter Score: before treatment vs 4 months FU
Comparison groups	Before treatment v At 4 months follow-up
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.084
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Sphincter Score: before treatment vs 7 months FU
Comparison groups	Before treatment v At 7 months follow-up
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.017
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Sphincter Score: before treatment vs 10 months FU
Comparison groups	Before treatment v At 10 months follow-up
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.018
Method	Wilcoxon (Mann-Whitney)

Primary: Change in the score in VAS scale

End point title	Change in the score in VAS scale

End point description:

VAS: Visual Analog Scale. This scale evaluates neuropathic pain. Efficacy was assessed by taking into account the variation in the scores on the different scales between the subject´s inclusion in the study and the scores obtained at the end of the follow-up period.

End point type	Primary

End point timeframe:

Between the subject´s inclusion in the study and the end of the follow-up period.

End point values	Before treatment	At 4 months follow-up	At 7 months follow-up	At 10 months follow-up
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	9	9	9	9
Units: Score				
arithmetic mean (standard deviation)	4.89 (± 2.37)	3.67 (± 2.00)	2.22 (± 2.05)	1.33 (± 2.03)

Statistical analyses

Statistical analysis title	Before treatment vs at 4 months FU
Comparison groups	Before treatment v At 4 months follow-up
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.011
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Before treatment vs at 7 months FU
Comparison groups	Before treatment v At 7 months follow-up

Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.012
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Before treatment vs at 10 months FU
Comparison groups	Before treatment v At 10 months follow-up
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.012
Method	Wilcoxon (Mann-Whitney)

Primary: Change in the score in PENN scale

End point title	Change in the score in PENN scale

End point description:

PENN scale measures the degree of spasms. Efficacy was assessed by taking into account the variation in the scores on the different scales between the subject´s inclusion in the study and the scores obtained at the end of the follow-up period.

End point type	Primary

End point timeframe:

Between the subject´s inclusion in the study and the end of the follow-up period.

End point values	Before treatment	At 4 months follow-up	At 7 months follow-up	At 10 months follow-up
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	9	9	9	9
Units: Score				
arithmetic mean (standard deviation)	1.33 (± 1.50)	1.22 (± 1.48)	1.11 (± 1.45)	1.11 (± 1.36)

Statistical analyses

Statistical analysis title	Before treatment vs at 4 months FU
Comparison groups	Before treatment v At 4 months follow-up
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.317
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Before treatment vs at 7 months FU
Comparison groups	Before treatment v At 7 months follow-up
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.157
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Before treatment vs at 10 months FU
Comparison groups	Before treatment v At 10 months follow-up
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.317
Method	Wilcoxon (Mann-Whitney)

Primary: Change in the score in Ashworth scale	
End point title	Change in the score in Ashworth scale
End point description:	
Ashworth scale measures the degree of spasticity. Efficacy was assessed by taking into account the variation in the scores on the different scales between the subject´s inclusion in the study and the scores obtained at the end of the follow-up period.	
End point type	Primary
End point timeframe:	
Between the subject´s inclusion in the study and the end of the follow-up period.	

End point values	Before treatment	At 4 months follow-up	At 7 months follow-up	At 10 months follow-up
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	9	9	9	9
Units: Score				
arithmetic mean (standard deviation)	1.44 (± 1.74)	1.33 (± 1.58)	1.11 (± 1.27)	1.11 (± 1.27)

Statistical analyses

Statistical analysis title	Before treatment vs at 4 months FU
Comparison groups	Before treatment v At 4 months follow-up

Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.317
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Before treatment vs at 7 months FU
Comparison groups	Before treatment v At 7 months follow-up
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.158
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Before treatment vs at 10 months FU
Comparison groups	Before treatment v At 10 months follow-up
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.158
Method	Wilcoxon (Mann-Whitney)

Primary: Change in the score in Geffner scale

End point title	Change in the score in Geffner scale

End point description:

Geffner scale was used for the study of bladder function. Efficacy was assessed by taking into account the variation in the scores on the different scales between the subject´s inclusion in the study and the scores obtained at the end of the follow-up period.

End point type	Primary

End point timeframe:

Between the subject´s inclusion in the study and the end of the follow-up period.

End point values	Before treatment	At 4 months follow-up	At 7 months follow-up	At 10 months follow-up
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	9	9	9	9
Units: Score				
arithmetic mean (standard deviation)	2.33 (± 1.66)	2.78 (± 1.48)	3.11 (± 1.83)	3.11 (± 1.83)

Statistical analyses

Statistical analysis title	Before treatment vs at 4 months FU
Comparison groups	Before treatment v At 4 months follow-up
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.084
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Before treatment vs at 7 months FU
Comparison groups	Before treatment v At 7 months follow-up
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.028
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Before treatment vs at 10 months FU
Comparison groups	Before treatment v At 10 months follow-up
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.028
Method	Wilcoxon (Mann-Whitney)

Primary: Change in the score in NBD scale

End point title	Change in the score in NBD scale

End point description:

NBD scale was used for the study of of neurogenic bowel dysfunction (NBD). Efficacy was assessed by taking into account the variation in the scores on the different scales between the subject´s inclusion in the study and the scores obtained at the end of the follow-up period.

End point type	Primary

End point timeframe:

Between the subject´s inclusion in the study and the end of the follow-up period.

End point values	Before treatment	At 4 months follow-up	At 7 months follow-up	At 10 months follow-up
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	9	9	9	9
Units: Score				
arithmetic mean (standard deviation)	13.89 (± 8.45)	8.33 (± 9.87)	7.11 (± 8.13)	5.78 (± 6.14)

Statistical analyses

Statistical analysis title	Before treatment vs at 4 months FU
Comparison groups	Before treatment v At 4 months follow-up
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.028
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Before treatment vs at 7 months FU
Comparison groups	Before treatment v At 7 months follow-up
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.018
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Before treatment vs at 10 months FU
Comparison groups	Before treatment v At 10 months follow-up
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.012
Method	Wilcoxon (Mann-Whitney)

Primary: Change in neurophysiological parameters: improvement in Somatosensory Evoked Potentials (SSEP)

End point title	Change in neurophysiological parameters: improvement in Somatosensory Evoked Potentials (SSEP)[2]

End point description:

End point type	Primary

End point timeframe:

Between the subject´s inclusion in the study and the end of the follow-up period.

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: A qualitative evaluation was performed, comparing the results with the baseline values.

End point values	Arm 1			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: Subjects				
Improvement in SSEP	6			
No improvement in SSEP	3			

Statistical analyses

No statistical analyses for this end point

Primary: Change in neurophysiological parameters: improvement in Motor Evoked Potentials (MEP)

End point title	Change in neurophysiological parameters: improvement in Motor Evoked Potentials (MEP)[3]

End point description:

End point type	Primary

End point timeframe:

Between the subject´s inclusion in the study and the end of the follow-up period.

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: A qualitative evaluation was performed, comparing the results with the baseline values.

End point values	Arm 1			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: Subjects				
Improvement in MEP	5			
No improvement in MEP	4			

Statistical analyses

No statistical analyses for this end point

Primary: Change in neurophysiological parameters: improvement in sensitivity conduction

End point title	Change in neurophysiological parameters: improvement in sensitivity conduction[4]

End point description:

End point type	Primary

End point timeframe:

Between the subject´s inclusion in the study and the end of the follow-up period.

Notes:

[4] - 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: A qualitative evaluation was performed, comparing the results with the baseline values.

End point values	Arm 1			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: Subjects				
Improvement	3			
No improvement	6			

Statistical analyses

No statistical analyses for this end point

Primary: Change in neurophysiological parameters: improvement in motor conduction

End point title	Change in neurophysiological parameters: improvement in motor conduction[5]

End point description:

End point type	Primary

End point timeframe:

Between the subject´s inclusion in the study and the end of the follow-up period.

Notes:

[5] - 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: A qualitative evaluation was performed, comparing the results with the baseline values.

End point values	Arm 1			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: Subjects				
Improvement	2			
No improvement	7			

Statistical analyses

No statistical analyses for this end point

Primary: Change in neurophysiological parameters: improvement in voluntary muscle contraction

End point title	Change in neurophysiological parameters: improvement in voluntary muscle contraction[6]

End point description:

End point type	Primary

End point timeframe:

Between the subject´s inclusion in the study and the end of the follow-up period.

Notes:

[6] - 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: A qualitative evaluation was performed, comparing the results with the baseline values.

End point values	Arm 1			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: Subjects				
Improvement	4			
No improvement	5			

Statistical analyses

No statistical analyses for this end point

Primary: Change in neurophysiological parameters: presence of infralesional activity muscle reinnervation

End point title	Change in neurophysiological parameters: presence of infralesional activity muscle reinnervation[7]

End point description:

End point type	Primary

End point timeframe:

Between the subject´s inclusion in the study and the end of the follow-up period.

Notes:

[7] - 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: A qualitative evaluation was performed, comparing the results with the baseline values.

End point values	Arm 1			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: Subjects				
Improvement	4			
No improvement	5			

Statistical analyses

No statistical analyses for this end point

Primary: Change in urodynamic studies: first sensation at filling

End point title	Change in urodynamic studies: first sensation at filling

End point description:

Urodynamic studies were performed using a Solar Luna equipment (Medical Measurement Systems Inc.).

End point type	Primary

End point timeframe:

Between the subject´s inclusion in the study and the end of the follow-up period.

End point values	Before treatment	At 10 months follow-up		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9		
Units: cc				
arithmetic mean (standard deviation)	275.33 (± 189.21)	244.56 (± 98.13)		

Statistical analyses

Statistical analysis title	Before treatment vs at 10 months FU
Comparison groups	Before treatment v At 10 months follow-up
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.952
Method	Wilcoxon (Mann-Whitney)

Primary: Change in urodynamic studies: maximum bladder capacity at filling

End point title	Change in urodynamic studies: maximum bladder capacity at filling

End point description:

Urodynamic studies were performed using a Solar Luna equipment (Medical Measurement Systems Inc.).

End point type	Primary

End point timeframe:

Between the subject´s inclusion in the study and the end of the follow-up period.

End point values	Before treatment	At 10 months follow-up		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9		
Units: cc				
arithmetic mean (standard deviation)	421.56 (± 175.73)	435.67 (± 138.20)		

Statistical analyses

Statistical analysis title	Before treatment vs at 10 months FU
Comparison groups	Before treatment v At 10 months follow-up
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.953
Method	Wilcoxon (Mann-Whitney)

Primary: Change in urodynamic studies: bladder compliance at filling

End point title	Change in urodynamic studies: bladder compliance at filling

End point description:

Urodynamic studies were performed using a Solar Luna equipment (Medical Measurement Systems Inc.).

End point type	Primary

End point timeframe:

Between the subject´s inclusion in the study and the end of the follow-up period.

End point values	Before treatment	At 10 months follow-up		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9		
Units: cc				
arithmetic mean (standard deviation)	31.61 (± 50.00)	24.26 (± 15.35)		

Statistical analyses

Statistical analysis title	Before treatment vs at 10 months FU
Comparison groups	Before treatment v At 10 months follow-up
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.515
Method	Wilcoxon (Mann-Whitney)

Primary: Change in urodynamic studies: volume	
End point title	Change in urodynamic studies: volume
End point description: Urodynamic studies were performed using a Solar Luna equipment (Medical Measurement Systems Inc.).	
End point type	Primary
End point timeframe: Between the subject´s inclusion in the study and the end of the follow-up period.	

End point values	Before treatment	At 10 months follow-up		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9		
Units: cc				
arithmetic mean (standard deviation)	41.67 (± 97.54)	75.56 (± 100.93)		

Statistical analyses

Statistical analysis title	Before treatment vs at 10 months FU
Comparison groups	Before treatment v At 10 months follow-up
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.018
Method	Wilcoxon (Mann-Whitney)

Primary: Change in urodynamic studies: time	
End point title	Change in urodynamic studies: time
End point description: Urodynamic studies were performed using a Solar Luna equipment (Medical Measurement Systems Inc.).	
End point type	Primary
End point timeframe: Between the subject´s inclusion in the study and the end of the follow-up period.	

End point values	Before treatment	At 10 months follow-up		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9		
Units: seconds				
arithmetic mean (standard deviation)	17.50 (± 42.00)	105.00 (± 104.47)		

Statistical analyses

Statistical analysis title	Before treatment vs at 10 months FU
Comparison groups	Before treatment v At 10 months follow-up
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.014
Method	Wilcoxon (Mann-Whitney)

Primary: Change in urodynamic studies: Q max

End point title	Change in urodynamic studies: Q max
End point description:	
Urodynamic studies were performed using a Solar Luna equipment (Medical Measurement Systems Inc.).	
End point type	Primary
End point timeframe:	
Between the subject´s inclusion in the study and the end of the follow-up period.	

End point values	Before treatment	At 10 months follow-up		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9		
Units: ml/seg				
arithmetic mean (standard deviation)	2.88 (± 6.08)	5.00 (± 4.50)		

Statistical analyses

Statistical analysis title	Before treatment vs at 10 months FU
Comparison groups	At 10 months follow-up v Before treatment

Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.178
Method	Wilcoxon (Mann-Whitney)

Primary: Change in urodynamic studies: detrusor pressure at filling

End point title	Change in urodynamic studies: detrusor pressure at filling

End point description:

Urodynamic studies were performed using a Solar Luna equipment (Medical Measurement Systems Inc.).

End point type	Primary

End point timeframe:

Between the subject´s inclusion in the study and the end of the follow-up period.

End point values	Before treatment	At 10 months follow-up		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9		
Units: cm H2O				
arithmetic mean (standard deviation)	11.00 (± 19.83)	35.11 (± 31.67)		

Statistical analyses

Statistical analysis title	Before treatment vs at 10 months FU
Comparison groups	Before treatment v At 10 months follow-up
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.097
Method	Wilcoxon (Mann-Whitney)

Primary: Change in urodynamic studies: postmictional residue

End point title	Change in urodynamic studies: postmictional residue

End point description:

Urodynamic studies were performed using a Solar Luna equipment (Medical Measurement Systems Inc.).

End point type	Primary

End point timeframe:

Between the subject´s inclusion in the study and the end of the follow-up period.

End point values	Before treatment	At 10 months follow-up		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9		
Units: cc				
arithmetic mean (standard deviation)	339.33 (± 248.91)	334.22 (± 182.01)		

Statistical analyses

Statistical analysis title	Before treatment vs at 10 months FU
Comparison groups	Before treatment v At 10 months follow-up
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.722
Method	Wilcoxon (Mann-Whitney)

Primary: Change in spinal cord morphology

End point title	Change in spinal cord morphology[8]

End point description:

The measurements were taken by a 3T imager (XR InteraAchieva 3T, Philips Healthcare). Lesions were studied on T1-and T2-weighted images and on MR-myelography images, using turbo-spin-echo sequences.
Qualitatively, it was observed that the patients did not present changes in spinal cord morphology.

End point type	Primary

End point timeframe:

Between the subject´s inclusion in the study and the end of the follow-up period.

Notes:

[8] - 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: A qualitative evaluation was performed, comparing the results with the baseline values.

End point values	Arm 1			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: mm				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in the levels of neurotrophins in cerebrospinal fluid: BDNF (brain-derived neurotrophic factor)

End point title	Change in the levels of neurotrophins in cerebrospinal fluid: BDNF (brain-derived neurotrophic factor)

End point description:

End point type	Secondary

End point timeframe:

Between the subject´s inclusion in the study and 7 month of follow-up.

End point values	Before treatment	At 4 months follow-up	At 7 months follow-up	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	7	9	8	
Units: pg/ml				
arithmetic mean (standard deviation)	2.67 (± 5.73)	30.26 (± 90.78)	54.70 (± 110.47)	

Statistical analyses

Statistical analysis title	Before treatment vs at 4 months FU
Comparison groups	Before treatment v At 4 months follow-up
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.662
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Before treatment vs at 7 months FU
Comparison groups	Before treatment v At 7 months follow-up
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.118
Method	Wilcoxon (Mann-Whitney)

Secondary: Change in the levels of neurotrophins in cerebrospinal fluid: GDNF (glial cell line-derived neurotrophic factor)

End point title	Change in the levels of neurotrophins in cerebrospinal fluid: GDNF (glial cell line-derived neurotrophic factor)

End point description:

End point type	Secondary

End point timeframe:

Between the subject´s inclusion in the study and 7 month of follow-up.

End point values	Before treatment	At 4 months follow-up	At 7 months follow-up	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	7	9	7	
Units: pg/ml				
arithmetic mean (standard deviation)	0.70 (± 0.64)	1.15 (± 1.15)	1.19 (± 1.00)	

Statistical analyses

Statistical analysis title	Before treatment vs at 4 months FU
Comparison groups	Before treatment v At 4 months follow-up
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.678
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Before treatment vs at 7 months FU
Comparison groups	Before treatment v At 7 months follow-up
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.097
Method	Wilcoxon (Mann-Whitney)

Secondary: Change in the levels of neurotrophins in cerebrospinal fluid: NGF (nerve growth factor)

End point title	Change in the levels of neurotrophins in cerebrospinal fluid: NGF (nerve growth factor)

End point description:

End point type	Secondary

End point timeframe:

Between the subject´s inclusion in the study and 7 month of follow-up.

End point values	Before treatment	At 4 months follow-up	At 7 months follow-up	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	7	9	7	
Units: pg/ml				
arithmetic mean (standard deviation)	2.42 (± 3.20)	7.83 (± 18.09)	12.39 (± 23.46)	

Statistical analyses

Statistical analysis title	Before treatment vs at 4 months FU
Comparison groups	Before treatment v At 4 months follow-up
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.504
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Before treatment vs at 7 months FU
Comparison groups	Before treatment v At 7 months follow-up
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.585
Method	Wilcoxon (Mann-Whitney)

Secondary: Change in the levels of neurotrophins in cerebrospinal fluid: NT3

End point title	Change in the levels of neurotrophins in cerebrospinal fluid: NT3

End point description:

End point type	Secondary

End point timeframe:

Between the subject´s inclusion in the study and 7 month of follow-up.

End point values	Before treatment	At 4 months follow-up	At 7 months follow-up	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	7	9	8	
Units: pg/ml				
arithmetic mean (standard deviation)	37.01 (± 4.70)	47.40 (± 33.30)	67.02 (± 58.74)	

Statistical analyses

Statistical analysis title	Before treatment vs at 4 months FU
Comparison groups	Before treatment v At 4 months follow-up
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.441
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Before treatment vs at 7 months FU
Comparison groups	Before treatment v At 7 months follow-up
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.066
Method	Wilcoxon (Mann-Whitney)

Secondary: Change in the levels of neurotrophins in cerebrospinal fluid: NT4

End point title	Change in the levels of neurotrophins in cerebrospinal fluid: NT4

End point description:

End point type	Secondary

End point timeframe:

Between the subject´s inclusion in the study and 7 month of follow-up.

End point values	Before treatment	At 4 months follow-up	At 7 months follow-up	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	7	9	8	
Units: pg/ml				
arithmetic mean (standard deviation)	9.39 (± 14.97)	11.33 (± 12.72)	10.30 (± 8.63)	

Statistical analyses

Statistical analysis title	Before treatment vs at 4 months FU
Comparison groups	Before treatment v At 4 months follow-up
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.097
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Before treatment vs at 7 months FU
Comparison groups	At 7 months follow-up v Before treatment
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.441
Method	Wilcoxon (Mann-Whitney)

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
During the entire clinical trial	
Adverse event reporting additional description:	
Adverse events were collected asking questions to the participants and performing general clinical examinations and neurological examinations.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups	
Reporting group title	Arm 1
Reporting group description:	
Treatment arm	

Serious adverse events	Arm 1		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 11 (9.09%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Follicle centre lymphoma, follicular grade I, II, III			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Arm 1		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 11 (36.36%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant ascites			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	2		
Nervous system disorders			

Sciatica	Additional description: Transitory sciatic pain		
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	3		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Pleural effusion	Additional description: Pleural and peritoneal effusion		
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Infections and infestations			
Urinary tract infection	Additional description: Urine infection		
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		

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

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

Number of patients studied and the variability of lesions.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29853256