



Clinical trial results:

A prospective, double-blind, randomised, placebo-controlled trial on the efficacy and safety of Neiromidin 20 mg tablets in the treatment of patients with lumbosacral radiculopathy

Summary

EudraCT number	2019-002632-90
Trial protocol	PL CZ LV BG
Global end of trial date	10 March 2023

Results information

Result version number	v1 (current)
This version publication date	07 June 2026
First version publication date	07 June 2026

Trial information

Trial identification

Sponsor protocol code	OF_NEIR_CT1
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	„Olainfarm“ AS
Sponsor organisation address	5 Rupnicu Street, Olaine, Latvia, LV-2114
Public contact	Olpha, Olpha, +371 67013708, olpha@olpha.eu
Scientific contact	Olpha, Olpha, +371 67013708, olpha@olpha.eu

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 May 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 March 2023
Global end of trial reached?	Yes
Global end of trial date	10 March 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the superiority of Neiromidin 20 mg tablets relative to placebo for the change in disability score (as assessed using Oswestry Disability Index [ODI]) from baseline to the end of 6-week treatment in patients with lumbosacral radiculopathy

Protection of trial subjects:

Specific measures - not applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 June 2021
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	Poland: 204
Country: Number of subjects enrolled	Bulgaria: 50
Country: Number of subjects enrolled	Czechia: 147
Country: Number of subjects enrolled	Latvia: 23
Worldwide total number of subjects	424
EEA total number of subjects	424

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)	418
From 65 to 84 years	6

85 years and over	0
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Subject disposition

Recruitment

Recruitment details:

All study subjects were recruited at the outpatient neurology clinics between July 2021 and December 2023.

Pre-assignment

Screening details:

The screening procedures were performed within a 1-7 day period before recruitment (randomization). All the results of screening procedures were required to be available before recruitment.

Pre-assignment period milestones

Number of subjects started	470 ^[1]
Intermediate milestone: Number of subjects	Enrolled: 424
Intermediate milestone: Number of subjects	Included in Full analysis set: 403
Number of subjects completed	403

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 26
Reason: Number of subjects	Lost of follow-up: 6
Reason: Number of subjects	Adverse event, non-fatal: 6
Reason: Number of subjects	Adverse event, serious fatal: 1
Reason: Number of subjects	Screening failure: 26
Reason: Number of subjects	Unspecified: 2

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 subjects screened for inclusion is provided for a pre-assignment period; the number of enrolled subjects is different.

Period 1

Period 1 title	Treatment (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

The study was double-blind. Patients were randomised to receive Neiromidin 20 mg tablets or matching placebo in a 1:1 allocation ratio using an adaptive randomisation algorithm with balancing for study/country/location factors. Subjects were centrally randomized using an Interactive Web Response Service. The specifications for generation of the randomization were prepared by an independent statistician.

Arms

Are arms mutually exclusive?	Yes
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Arm title	Active
Arm description:	
Full analysis set	
Arm type	Experimental
Investigational medicinal product name	Neiromidin 20 mg tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
1 (one) Neiromidin 20 mg tablet three times a day for 6 weeks (42 days).	
Arm title	Placebo
Arm description:	
Full analysis set	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Placebo (three times a day) tablets for 6 weeks (42 days).	

Number of subjects in period 1^[2]	Active	Placebo
Started	206	197
Completed	206	197

Notes:

[2] - The number of subjects reported to be in the baseline 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 worldwide number of enrolled subjects refers to the ITT population. The primary analysis of all efficacy variables was performed and reported on the Full analysis set, thus the FUL is used as a baseline.

Baseline characteristics

Reporting groups

Reporting group title	Active
Reporting group description:	
Full analysis set	
Reporting group title	Placebo
Reporting group description:	
Full analysis set	

Reporting group values	Active	Placebo	Total
Number of subjects	206	197	403
Age categorical			
Units: Subjects			
Adults (18-64 years)	203	194	397
From 65-84 years	3	3	6
Age continuous			
Units: years			
arithmetic mean	49.8	50.7	
standard deviation	± 9.3	± 9.5	-
Gender categorical			
Units: Subjects			
Female	116	122	238
Male	90	75	165
Race			
Units: Subjects			
White	206	197	403
Body mass index			
Units: kg/m2			
arithmetic mean	28.55	28.12	
standard deviation	± 4.69	± 4.87	-

Subject analysis sets

Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis
Subject analysis set description:	
Safety analysis set	

Reporting group values	Safety analysis set		
Number of subjects	423		
Age categorical			
Units: Subjects			
Adults (18-64 years)	417		
From 65-84 years	6		
Age continuous			
Units: years			
arithmetic mean	50.1		

standard deviation	± 9.5		
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Gender categorical			
Units: Subjects			
Female	245		
Male	178		
Race			
Units: Subjects			
White	423		
Body mass index			
Units: kg/m2			
arithmetic mean	28.33		
standard deviation	± 4.78		

End points

End points reporting groups

Reporting group title	Active
Reporting group description:	
Full analysis set	
Reporting group title	Placebo
Reporting group description:	
Full analysis set	
Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis
Subject analysis set description:	
Safety analysis set	

Primary: Oswestry Disability Index (ODI)

End point title	Oswestry Disability Index (ODI)
End point description:	
Change in total ODI score from baseline (Day 0) to Week 6. Full analysis set.	
End point type	Primary
End point timeframe:	
Baseline (Day 0) to Week 6	

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	197		
Units: Points				
least squares mean (confidence interval 95%)	-12.20 (-13.96 to -10.45)	-11.20 (-12.98 to -9.42)		

Statistical analyses

Statistical analysis title	ANCOVA
Comparison groups	Active v Placebo
Number of subjects included in analysis	403
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	> 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.51
upper limit	1.5

Notes:

[1] - Results display model-based mean difference between active and placebo with terms for treatment and ODI baseline value. Variable tested at a 5% significance level.

Primary: Oswestry Disability Index (ODI) 2

End point title	Oswestry Disability Index (ODI) 2
End point description:	Change in total ODI score, excluding subjects with NSAID or rescue medication within 2 days prior to Day 42
End point type	Primary
End point timeframe:	From baseline to Week 6

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	197		
Units: Points				
least squares mean (confidence interval 95%)	-14.70 (-17.64 to -11.77)	-11.04 (-13.85 to -8.23)		

Statistical analyses

Statistical analysis title	ANCOVA
Comparison groups	Active v Placebo
Number of subjects included in analysis	403
Analysis specification	Post-hoc
Analysis type	superiority ^[2]
P-value	= 0.0271
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-3.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.91
upper limit	-0.42

Notes:

[2] - Results display model-based mean difference between active and placebo with terms for treatment, country and ODI baseline value. Variable tested at a 5% significance level.

Secondary: Leg pain

End point title	Leg pain
End point description:	Change in leg pain intensity on the NRS
End point type	Secondary
End point timeframe:	From baseline to Week 6

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	197		
Units: Points				
least squares mean (confidence interval 95%)	-2.59 (-2.92 to -2.26)	-2.72 (-3.05 to -2.38)		

Statistical analyses

Statistical analysis title	ANCOVA
Comparison groups	Active v Placebo
Number of subjects included in analysis	403
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 ^[3]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.35
upper limit	0.59

Notes:

[3] - Variable tested at a 5% significance level

Secondary: Low back pain

End point title	Low back pain
End point description:	
Change in low back pain intensity on the NRS	
End point type	Secondary
End point timeframe:	
From baseline to Week 3	

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	197		
Units: Points				
least squares mean (confidence interval 95%)	-1.47 (-1.73 to -1.21)	-1.62 (-1.88 to -1.36)		

Statistical analyses

Statistical analysis title	ANCOVA
Comparison groups	Active v Placebo
Number of subjects included in analysis	403
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 ^[4]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.22
upper limit	0.52

Notes:

[4] - Variable tested at a 5% significance level

Secondary: Low back pain 2

End point title	Low back pain 2
End point description:	
Change in low back pain intensity on the NRS	
End point type	Secondary
End point timeframe:	
From baseline to Week 6	

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	197		
Units: Points				
least squares mean (confidence interval 95%)	-2.25 (-2.56 to -1.94)	-2.40 (-2.72 to -2.09)		

Statistical analyses

Statistical analysis title	ANCOVA
Comparison groups	Active v Placebo

Number of subjects included in analysis	403
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 ^[5]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.29
upper limit	0.6

Notes:

[5] - Variable tested at a 5% significance level

Secondary: Sensory nerve conduction

End point title	Sensory nerve conduction
End point description:	
Change in Sensory Conduction Velocity (SCV) in sensory nerve (sural), affected leg	
End point type	Secondary
End point timeframe:	
From baseline to Week 6	

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	197		
Units: m/s				
least squares mean (confidence interval 95%)	0.25 (-0.94 to 1.44)	0.83 (-0.34 to 1.99)		

Statistical analyses

Statistical analysis title	ANCOVA
Comparison groups	Active v Placebo
Number of subjects included in analysis	403
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 ^[6]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.24
upper limit	1.09

Notes:

[6] - Variable tested at a 5% significance level

Secondary: Sensory nerve conduction 2

End point title	Sensory nerve conduction 2
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End point description:

Change in Peak Latency in sensory nerve (sural), affected leg

End point type	Secondary
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End point timeframe:

From baseline to Week 6

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	197		
Units: ms				
least squares mean (confidence interval 95%)	-0.39 (-0.56 to -0.21)	-0.35 (-0.52 to -0.18)		

Statistical analyses

Statistical analysis title	ANCOVA
Comparison groups	Active v Placebo
Number of subjects included in analysis	403
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [7]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.28
upper limit	0.21

Notes:

[7] - Variable tested at a 5% significance level

Secondary: Sensory nerve conduction 3

End point title	Sensory nerve conduction 3
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End point description:

Change in Distal Sensory Nerve Action Potential (SNAP) Amplitude in sensory nerve (sural), affected leg

End point type	Secondary
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End point timeframe:

From baseline to Week 6

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	197		
Units: μV				
least squares mean (confidence interval 95%)	0.41 (-1.70 to 2.53)	1.05 (-1.02 to 3.13)		

Statistical analyses

Statistical analysis title	ANCOVA
Comparison groups	Active v Placebo
Number of subjects included in analysis	403
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [8]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.61
upper limit	2.33

Notes:

[8] - Variable tested at a 5% significance level

Secondary: Motor nerve conduction

End point title	Motor nerve conduction
End point description:	Change in Motor Conduction Velocity (MCV) in motor nerve (peroneal), affected leg
End point type	Secondary
End point timeframe:	From baseline to Week 6

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	197		
Units: m/s				
least squares mean (confidence interval 95%)	-0.30 (-1.19 to 0.59)	0.01 (-0.87 to 0.89)		

Statistical analyses

Statistical analysis title	ANCOVA
Comparison groups	Active v Placebo
Number of subjects included in analysis	403
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [9]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.56
upper limit	0.94

Notes:

[9] - Variable tested at a 5% significance level

Secondary: Motor nerve conduction 2

End point title	Motor nerve conduction 2
End point description:	
Change in Motor Conduction Velocity (MCV) in motor nerve (tibial), affected leg	
End point type	Secondary
End point timeframe:	
From baseline to Week 6	

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	197		
Units: ms				
least squares mean (confidence interval 95%)	-0.64 (-1.45 to 0.17)	-0.53 (-1.34 to 0.27)		

Statistical analyses

Statistical analysis title	ANCOVA
Comparison groups	Active v Placebo

Number of subjects included in analysis	403
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 ^[10]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.25
upper limit	1.04

Notes:

[10] - Variable tested at a 5% significance level

Secondary: Motor nerve conduction 3

End point title	Motor nerve conduction 3
End point description:	
Change in Distal Motor Latency (DML) in motor nerve (peroneal), affected leg	
End point type	Secondary
End point timeframe:	
From baseline to Week 6	

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	197		
Units: µV				
least squares mean (confidence interval 95%)	0.06 (-0.26 to 0.38)	-0.45 (-0.76 to -0.13)		

Statistical analyses

Statistical analysis title	ANCOVA
Comparison groups	Active v Placebo
Number of subjects included in analysis	403
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 ^[11]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.06
upper limit	0.96

Notes:

[11] - Variable tested at a 5% significance level

Secondary: Motor nerve conduction 4

End point title	Motor nerve conduction 4
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End point description:

Change in Distal Motor Latency (DML) in motor nerve (tibial), affected leg

End point type	Secondary
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End point timeframe:

From baseline to Week 6

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	197		
Units: ms				
least squares mean (confidence interval 95%)	-0.12 (-0.60 to 0.36)	-0.22 (-0.69 to 0.25)		

Statistical analyses

Statistical analysis title	ANCOVA
Comparison groups	Active v Placebo
Number of subjects included in analysis	403
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 ^[12]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.58
upper limit	0.77

Notes:

[12] - Variable tested at a 5% significance level

Secondary: Motor nerve conduction 5

End point title	Motor nerve conduction 5
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End point description:

Change in Distal Compound Muscle Action Potential (CMAP) Amplitude in motor nerve (peroneal), affected leg

End point type	Secondary
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End point timeframe:

From baseline to Week 6

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	197		
Units: mV				
least squares mean (confidence interval 95%)	-0.04 (-0.61 to 0.53)	-0.11 (-0.67 to 0.45)		

Statistical analyses

Statistical analysis title	ANCOVA
Comparison groups	Active v Placebo
Number of subjects included in analysis	403
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 ^[13]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.27
upper limit	0.87

Notes:

[13] - Variable tested at a 5% significance level

Secondary: Motor nerve conduction 6

End point title	Motor nerve conduction 6
End point description:	Change in Distal Compound Muscle Action Potential (CMAP) Amplitude in motor nerve (tibial), affected leg
End point type	Secondary
End point timeframe:	From baseline to Week 6

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	197		
Units: mV				
least squares mean (confidence interval 95%)	0.11 (-0.77 to 0.99)	-0.31 (-1.18 to 0.56)		

Statistical analyses

Statistical analysis title	ANCOVA
Comparison groups	Active v Placebo
Number of subjects included in analysis	403
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 ^[14]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.82
upper limit	1.66

Notes:

[14] - Variable tested at a 5% significance level

Secondary: Motor nerve conduction 7

End point title	Motor nerve conduction 7
End point description:	
Change in late responses (minimal F-wave latency), in motor nerve (peroneal), affected leg	
End point type	Secondary
End point timeframe:	
From baseline to Week 6	

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	197		
Units: m/s				
least squares mean (confidence interval 95%)	0.44 (-0.34 to 1.21)	-0.33 (-1.11 to 0.46)		

Statistical analyses

Statistical analysis title	ANCOVA
Comparison groups	Active v Placebo

Number of subjects included in analysis	403
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 ^[15]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.34
upper limit	1.87

Notes:

[15] - Variable tested at a 5% significance level

Secondary: Motor nerve conduction 8

End point title	Motor nerve conduction 8
End point description:	
Change in late responses (minimal F-wave latency), in motor nerve (tibial), affected leg	
End point type	Secondary
End point timeframe:	
From baseline to Week 6	

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	197		
Units: m/s				
least squares mean (confidence interval 95%)	0.31 (-0.26 to 0.87)	-0.17 (-0.72 to 0.39)		

Statistical analyses

Statistical analysis title	ANCOVA
Comparison groups	Active v Placebo
Number of subjects included in analysis	403
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 ^[16]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.32
upper limit	1.26

Notes:

[16] - Variable tested at a 5% significance level

Secondary: Muscle strength (MRC scale)

End point title	Muscle strength (MRC scale)
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End point description:

Change in muscle strength, plantar flexors - soleus, affected side

End point type	Secondary
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End point timeframe:

From baseline to Week 3

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	197		
Units: n/a	206	197		

Statistical analyses

Statistical analysis title	GEE
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Statistical analysis description:

Results display comparison between active and placebo and are based on a generalised estimating equation (GEE) for a repeated proportional odds model including treatment, time and treatment*time interaction and muscle strength at baseline value. Variable tested at a 5% significance level.

Comparison groups	Active v Placebo
Number of subjects included in analysis	403
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Sign test
Parameter estimate	Odds ratio (OR)
Point estimate	1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	1.99

Secondary: Muscle strength (MRC scale) 2

End point title	Muscle strength (MRC scale) 2
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End point description:

Change in muscle strength, plantar flexors - soleus, affected side

End point type	Secondary
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End point timeframe:
From baseline to Week 6

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	197		
Units: n/a	206	197		

Statistical analyses

Statistical analysis title	GEE
Statistical analysis description: Results display comparison between active and placebo and are based on a generalised estimating equation (GEE) for a repeated proportional odds model including treatment, time and treatment*time interaction and muscle strength at baseline value. Variable tested at a 5% significance level.	
Comparison groups	Active v Placebo
Number of subjects included in analysis	403
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Sign test
Parameter estimate	Odds ratio (OR)
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	1.88

Secondary: Muscle strength (MRC scale) 3

End point title	Muscle strength (MRC scale) 3
End point description: Change in muscle strength, plantar flexors - gastrocnemius, affected side	
End point type	Secondary
End point timeframe: From baseline to Week 3	

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	197		
Units: n/a	206	197		

Statistical analyses

Statistical analysis title	GEE
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Statistical analysis description:

Results display comparison between active and placebo and are based on a generalised estimating equation (GEE) for a repeated proportional odds model including treatment, time and treatment*time interaction and muscle strength at baseline value. Variable tested at a 5% significance level.

Comparison groups	Placebo v Active
Number of subjects included in analysis	403
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Sign test
Parameter estimate	Odds ratio (OR)
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	1.62

Secondary: Muscle strength (MRC scale) 4

End point title	Muscle strength (MRC scale) 4
End point description:	Change in muscle strength, plantar flexors - gastrocnemius, affected side
End point type	Secondary
End point timeframe:	From baseline to Week 6

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	197		
Units: n/a	206	197		

Statistical analyses

Statistical analysis title	GEE
Statistical analysis description:	
Results display comparison between active and placebo and are based on a generalised estimating equation (GEE) for a repeated proportional odds model including treatment, time and treatment*time interaction and muscle strength at baseline value. Variable tested at a 5% significance level.	
Comparison groups	Active v Placebo
Number of subjects included in analysis	403
Analysis specification	Pre-specified
Analysis type	
P-value	> 0.05
Method	Sign test
Parameter estimate	Odds ratio (OR)
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	1.72

Secondary: Muscle strength (MRC scale) 5

End point title	Muscle strength (MRC scale) 5
End point description:	
Change in muscle strength, ankle dorsiflexor - tibialis anterior, affected side	
End point type	Secondary
End point timeframe:	
From baseline to Week 3	

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	197		
Units: n/a	206	197		

Statistical analyses

Statistical analysis title	GEE
Statistical analysis description:	
Results display comparison between active and placebo and are based on a generalised estimating equation (GEE) for a repeated proportional odds model including treatment, time and treatment*time interaction and muscle strength at baseline value. Variable tested at a 5% significance level.	
Comparison groups	Active v Placebo

Number of subjects included in analysis	403
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Sign test
Parameter estimate	Odds ratio (OR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	1.74

Secondary: Muscle strength (MRC scale) 6

End point title	Muscle strength (MRC scale) 6
End point description:	
Change in muscle strength, ankle dorsiflexor - tibialis anterior, affected side	
End point type	Secondary
End point timeframe:	
From baseline to Week 6	

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	197		
Units: n/a	206	197		

Statistical analyses

Statistical analysis title	GEE
Statistical analysis description:	
Results display comparison between active and placebo and are based on a generalised estimating equation (GEE) for a repeated proportional odds model including treatment, time and treatment*time interaction and muscle strength at baseline value. Variable tested at a 5% significance level.	
Comparison groups	Active v Placebo
Number of subjects included in analysis	403
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Sign test
Parameter estimate	Odds ratio (OR)
Point estimate	0.87

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	1.7

Secondary: Muscle strength (MRC scale) 7

End point title	Muscle strength (MRC scale) 7
End point description:	
Change in muscle strength, great toe extensor - hallucis longus, affected side	
End point type	Secondary
End point timeframe:	
From baseline to Week 3	

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	197		
Units: n/a	206	197		

Statistical analyses

Statistical analysis title	GEE
Statistical analysis description:	
Results display comparison between active and placebo and are based on a generalised estimating equation (GEE) for a repeated proportional odds model including treatment, time and treatment*time interaction and muscle strength at baseline value. Variable tested at a 5% significance level.	
Comparison groups	Placebo v Active
Number of subjects included in analysis	403
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Sign test
Parameter estimate	Odds ratio (OR)
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	1.34

Secondary: Muscle strength (MRC scale) 8

End point title	Muscle strength (MRC scale) 8
End point description:	
Change in muscle strength, great toe extensor - hallucis longus, affected side	
End point type	Secondary
End point timeframe:	
From baseline to Week 6	

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	197		
Units: n/a	206	197		

Statistical analyses

Statistical analysis title	GEE
Statistical analysis description:	
Results display comparison between active and placebo and are based on a generalised estimating equation (GEE) for a repeated proportional odds model including treatment, time and treatment*time interaction and muscle strength at baseline value. Variable tested at a 5% significance level.	
Comparison groups	Active v Placebo
Number of subjects included in analysis	403
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Sign test
Parameter estimate	Odds ratio (OR)
Point estimate	0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.35
upper limit	1.22

Secondary: Sensitivity

End point title	Sensitivity
End point description:	
Change in sensitivity (Pinprick and light touch sensation) for S1 (lateral heel) dermatome	
End point type	Secondary
End point timeframe:	
From baseline to Week 3	

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	197		
Units: n/a	206	197		

Statistical analyses

Statistical analysis title	GEE
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Statistical analysis description:

Results display comparison between active and placebo and are based on a generalised estimating equation (GEE) for a repeated proportional odds model including treatment, time and treatment*time interaction and muscle strength at baseline value. Variable tested at a 5% significance level.

Comparison groups	Active v Placebo
Number of subjects included in analysis	403
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Sign test
Parameter estimate	Odds ratio (OR)
Point estimate	0.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.16
upper limit	1.31

Secondary: Sensitivity 2

End point title	Sensitivity 2
End point description:	
Change in sensitivity (Pinprick and light touch sensation) for S1 (lateral heel) dermatome	
End point type	Secondary
End point timeframe:	
From baseline to Week 6	

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	197		
Units: n/a	206	197		

Statistical analyses

Statistical analysis title	GEE
Statistical analysis description:	
Results display comparison between active and placebo and are based on a generalised estimating equation (GEE) for a repeated proportional odds model including treatment, time and treatment*time interaction and muscle strength at baseline value. Variable tested at a 5% significance level.	
Comparison groups	Active v Placebo
Number of subjects included in analysis	403
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Sign test
Parameter estimate	Odds ratio (OR)
Point estimate	0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	4.81

Secondary: Sensitivity 3

End point title	Sensitivity 3
End point description:	
Change in sensitivity (Pinprick and light touch sensation) for L5 (dorsum of the foot at the third metatarsal phalangeal joint) dermatome	
End point type	Secondary
End point timeframe:	
From baseline to Week 3	

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	197		
Units: n/a	206	197		

Statistical analyses

Statistical analysis title	GEE
Statistical analysis description:	
Results display comparison between active and placebo and are based on a generalised estimating equation (GEE) for a repeated proportional odds model including treatment, time and treatment*time interaction and muscle strength at baseline value. Variable tested at a 5% significance level.	
Comparison groups	Active v Placebo

Number of subjects included in analysis	403
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Sign test
Parameter estimate	Odds ratio (OR)
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	1.79

Secondary: Sensitivity 4

End point title	Sensitivity 4
End point description:	
Change in sensitivity (Pinprick and light touch sensation) for L5 (dorsum of the foot at the third metatarsal phalangeal joint) dermatome	
End point type	Secondary
End point timeframe:	
From baseline to Week 6	

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	197		
Units: n/a	206	197		

Statistical analyses

Statistical analysis title	GEE
Statistical analysis description:	
Results display comparison between active and placebo and are based on a generalised estimating equation (GEE) for a repeated proportional odds model including treatment, time and treatment*time interaction and muscle strength at baseline value. Variable tested at a 5% significance level.	
Comparison groups	Active v Placebo
Number of subjects included in analysis	403
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Sign test
Parameter estimate	Odds ratio (OR)
Point estimate	0.94

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	1.77

Secondary: Reflexes

End point title	Reflexes
End point description:	
Change in Achilles reflexes, affected leg	
End point type	Secondary
End point timeframe:	
From baseline to Week 3	

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	197		
Units: n/a	206	197		

Statistical analyses

Statistical analysis title	GEE
Statistical analysis description:	
Results display comparison between active and placebo and are based on a generalised estimating equation (GEE) for a repeated proportional odds model including treatment, time and treatment*time interaction and muscle strength at baseline value. Variable tested at a 5% significance level.	
Comparison groups	Active v Placebo
Number of subjects included in analysis	403
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Sign test
Parameter estimate	Odds ratio (OR)
Point estimate	1.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	1.65

Secondary: Reflexes 2

End point title	Reflexes 2
End point description: Change in Achilles reflexes, affected leg	
End point type	Secondary
End point timeframe: From baseline to Week 6	

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	197		
Units: n/a	206	197		

Statistical analyses

Statistical analysis title	GEE
Statistical analysis description: Results display comparison between active and placebo and are based on a generalised estimating equation (GEE) for a repeated proportional odds model including treatment, time and treatment*time interaction and muscle strength at baseline value. Variable tested at a 5% significance level.	
Comparison groups	Active v Placebo
Number of subjects included in analysis	403
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Sign test
Parameter estimate	Odds ratio (OR)
Point estimate	1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	1.73

Secondary: Patient Global Impression of Change

End point title	Patient Global Impression of Change
End point description: Statistical analysis of PGIC response	
End point type	Secondary
End point timeframe: From baseline to Week 3	

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	197		
Units: n/a	206	197		

Statistical analyses

Statistical analysis title	GLMM
Statistical analysis description:	
Results display comparison between active and placebo and are based on the logistic generalised linear mixed model (GLMM) using PROC GENMOD. The model includes the fixed effects treatment, visit, treatment by visit interaction assuming an unstructured correlation matrix. Variable tested at a 5% significance level.	
Comparison groups	Active v Placebo
Number of subjects included in analysis	403
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Sign test
Parameter estimate	Odds ratio (OR)
Point estimate	1.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	3.73

Secondary: Patient Global Impression of Change 2

End point title	Patient Global Impression of Change 2
End point description:	
Statistical analysis of PGIC response	
End point type	Secondary
End point timeframe:	
From baseline to Week 6	

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	197		
Units: n/a	206	197		

Statistical analyses

Statistical analysis title	GLMM
Statistical analysis description:	
Results display comparison between active and placebo and are based on the logistic generalised linear mixed model (GLMM) using PROC GENMOD. The model includes the fixed effects treatment, visit, treatment by visit interaction assuming an unstructured correlation matrix. Variable tested at a 5% significance level.	
Comparison groups	Active v Placebo
Number of subjects included in analysis	403
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Sign test
Parameter estimate	Odds ratio (OR)
Point estimate	1.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	4.93

Secondary: Quality of life (EQ-5D-5L)

End point title	Quality of life (EQ-5D-5L)
End point description:	
Change in EQ-5D-5L Mobility dimension	
End point type	Secondary
End point timeframe:	
From baseline to Week 6	

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	197		
Units: n/a	206	197		

Statistical analyses

Statistical analysis title	Proportional odds model
Statistical analysis description:	
Results display comparison between active and placebo and are based on a proportional odds model including treatment and baseline value. Variable tested at a 5% significance level	
Comparison groups	Active v Placebo

Number of subjects included in analysis	403
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Sign test
Parameter estimate	Odds ratio (OR)
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	1.3

Secondary: Quality of life (EQ-5D-5L) 2

End point title	Quality of life (EQ-5D-5L) 2
End point description:	
Change in EQ-5D-5L Self-care dimension	
End point type	Secondary
End point timeframe:	
From baseline to Week 6	

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	197		
Units: n/a	206	197		

Statistical analyses

Statistical analysis title	Proportional odds model
Statistical analysis description:	
Results display comparison between active and placebo and are based on a proportional odds model including treatment and baseline value. Variable tested at a 5% significance level.	
Comparison groups	Active v Placebo
Number of subjects included in analysis	403
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Sign test
Parameter estimate	Odds ratio (OR)
Point estimate	0.93

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	1.37

Secondary: Quality of life (EQ-5D-5L) 3

End point title	Quality of life (EQ-5D-5L) 3
End point description:	
Change in EQ-5D-5L Usual activities dimension	
End point type	Secondary
End point timeframe:	
From baseline to Week 6	

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	197		
Units: n/a	206	197		

Statistical analyses

Statistical analysis title	Proportional odds model
Statistical analysis description:	
Results display comparison between active and placebo and are based on a proportional odds model including treatment and baseline value. Variable tested at a 5% significance level.	
Comparison groups	Active v Placebo
Number of subjects included in analysis	403
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Sign test
Parameter estimate	Odds ratio (OR)
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	1.54

Secondary: Quality of life (EQ-5D-5L) 4

End point title	Quality of life (EQ-5D-5L) 4
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End point description:	
Change in EQ-5D-5L Pain/discomfort dimension	
End point type	Secondary
End point timeframe:	
From baseline to Week 6	

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	197		
Units: n/a	206	197		

Statistical analyses

Statistical analysis title	Proportional odds model
Statistical analysis description:	
Results display comparison between active and placebo and are based on a proportional odds model including treatment and baseline value. Variable tested at a 5% significance level.	
Comparison groups	Active v Placebo
Number of subjects included in analysis	403
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Sign test
Parameter estimate	Odds ratio (OR)
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1.44

Secondary: Quality of life (EQ-5D-5L) 5

End point title	Quality of life (EQ-5D-5L) 5
End point description:	
Change in EQ-5D-5L Anxiety/depression dimension	
End point type	Secondary
End point timeframe:	
From baseline to Week 6	

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	197		
Units: n/a	206	197		

Statistical analyses

Statistical analysis title	Proportional odds model
Statistical analysis description:	
Results display comparison between active and placebo and are based on a proportional odds model including treatment and baseline value. Variable tested at a 5% significance level.	
Comparison groups	Active v Placebo
Number of subjects included in analysis	403
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Sign test
Parameter estimate	Odds ratio (OR)
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	1.61

Secondary: Quality of life (EQ-5D-5L) 6

End point title	Quality of life (EQ-5D-5L) 6
End point description:	
Change in EQ VAS score	
End point type	Secondary
End point timeframe:	
From baseline to Week 6	

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	197		
Units: score				
least squares mean (confidence interval 95%)	8.88 (6.75 to 11.02)	11.44 (9.28 to 13.60)		

Statistical analyses

Statistical analysis title	ANCOVA
Comparison groups	Active v Placebo
Number of subjects included in analysis	403
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 ^[17]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-2.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.6
upper limit	0.48

Notes:

[17] - Variable tested at a 5% significance level

Secondary: Leg pain W3

End point title	Leg pain W3
End point description:	
Change in leg pain intensity on the NRS	
End point type	Secondary
End point timeframe:	
From baseline to Week 3	

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	197		
Units: Points				
least squares mean (confidence interval 95%)	-1.66 (-1.92 to -1.40)	-1.90 (-2.17 to -1.64)		

Statistical analyses

Statistical analysis title	ANCOVA
Comparison groups	Active v Placebo
Number of subjects included in analysis	403
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 ^[18]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.24

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.13
upper limit	0.62

Notes:

[18] - Variable tested at a 5% significance level

Other pre-specified: Serum BDNF

End point title	Serum BDNF
End point description:	
Change in serum BDNF level	
End point type	Other pre-specified
End point timeframe:	
From baseline to Week 6	

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	180	167		
Units: ng/ml				
least squares mean (confidence interval 95%)	3.69 (-0.63 to 8.02)	4.72 (0.23 to 9.21)		

Statistical analyses

Statistical analysis title	ANCOVA
Comparison groups	Active v Placebo
Number of subjects included in analysis	347
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 ^[19]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.26
upper limit	5.22

Notes:

[19] - Variable tested at a 5% significance level

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From informed consent date to the follow-up evaluation (30 days after the end of the treatment).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.1
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Reporting groups

Reporting group title	Active
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Reporting group description:

All subjects in active group who have taken at least one dose of the IMP.

Reporting group title	Placebo
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Reporting group description:

All subjects in placebo group who have taken at least one dose of the IMP.

Serious adverse events	Active	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 206 (0.49%)	4 / 197 (2.03%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events		1	
Injury, poisoning and procedural complications			
Lower limb fracture			
subjects affected / exposed	0 / 206 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 206 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	0 / 206 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 206 (0.49%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Respiratory tract infection			
subjects affected / exposed	0 / 206 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Active	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	80 / 206 (38.83%)	67 / 197 (34.01%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 206 (1.94%)	1 / 197 (0.51%)	
occurrences (all)	6	1	
Thrombosis			
subjects affected / exposed	1 / 206 (0.49%)	0 / 197 (0.00%)	
occurrences (all)	1	0	
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	1 / 206 (0.49%)	0 / 197 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 206 (0.97%)	3 / 197 (1.52%)	
occurrences (all)	2	4	
Pain			
subjects affected / exposed	2 / 206 (0.97%)	1 / 197 (0.51%)	
occurrences (all)	2	2	
Chest pain			

subjects affected / exposed occurrences (all)	0 / 206 (0.00%) 0	1 / 197 (0.51%) 1	
Malaise subjects affected / exposed occurrences (all)	0 / 206 (0.00%) 0	1 / 197 (0.51%) 1	
Oedema peripheral subjects affected / exposed occurrences (all)	0 / 206 (0.00%) 0	1 / 197 (0.51%) 1	
Pyrexia subjects affected / exposed occurrences (all)	0 / 206 (0.00%) 0	1 / 197 (0.51%) 1	
Swelling subjects affected / exposed occurrences (all)	1 / 206 (0.49%) 1	0 / 197 (0.00%) 0	
Reproductive system and breast disorders Dysmenorrhoea subjects affected / exposed occurrences (all)	1 / 206 (0.49%) 1	0 / 197 (0.00%) 0	
Erectile dysfunction subjects affected / exposed occurrences (all)	0 / 206 (0.00%) 0	1 / 197 (0.51%) 1	
Vaginal haemorrhage subjects affected / exposed occurrences (all)	1 / 206 (0.49%) 1	0 / 197 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	2 / 206 (0.97%) 2	0 / 197 (0.00%) 0	
Dyspnoea subjects affected / exposed occurrences (all)	0 / 206 (0.00%) 0	2 / 197 (1.02%) 2	
Dry throat subjects affected / exposed occurrences (all)	1 / 206 (0.49%) 1	0 / 197 (0.00%) 0	
Oropharyngeal pain			

subjects affected / exposed occurrences (all)	0 / 206 (0.00%) 0	1 / 197 (0.51%) 1	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	4 / 206 (1.94%)	0 / 197 (0.00%)	
occurrences (all)	4	0	
Agitation			
subjects affected / exposed	2 / 206 (0.97%)	0 / 197 (0.00%)	
occurrences (all)	2	0	
Sleep disorder			
subjects affected / exposed	0 / 206 (0.00%)	2 / 197 (1.02%)	
occurrences (all)	0	2	
Anxiety			
subjects affected / exposed	0 / 206 (0.00%)	1 / 197 (0.51%)	
occurrences (all)	0	1	
Depressed mood			
subjects affected / exposed	0 / 206 (0.00%)	1 / 197 (0.51%)	
occurrences (all)	0	1	
Libido decreased			
subjects affected / exposed	1 / 206 (0.49%)	0 / 197 (0.00%)	
occurrences (all)	1	0	
Investigations			
Blood glucose increased			
subjects affected / exposed	1 / 206 (0.49%)	1 / 197 (0.51%)	
occurrences (all)	1	1	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 206 (0.00%)	1 / 197 (0.51%)	
occurrences (all)	0	1	
Blood glucose abnormal			
subjects affected / exposed	0 / 206 (0.00%)	1 / 197 (0.51%)	
occurrences (all)	0	1	
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 206 (0.00%)	1 / 197 (0.51%)	
occurrences (all)	0	1	
Gamma-glutamyltransferase increased			

subjects affected / exposed occurrences (all)	1 / 206 (0.49%) 1	0 / 197 (0.00%) 0	
Hepatic enzyme increased subjects affected / exposed occurrences (all)	1 / 206 (0.49%) 1	0 / 197 (0.00%) 0	
Prostatic specific antigen increased subjects affected / exposed occurrences (all)	0 / 206 (0.00%) 0	1 / 197 (0.51%) 1	
Injury, poisoning and procedural complications			
Fall subjects affected / exposed occurrences (all)	0 / 206 (0.00%) 0	2 / 197 (1.02%) 3	
Contusion subjects affected / exposed occurrences (all)	0 / 206 (0.00%) 0	1 / 197 (0.51%) 1	
Forearm fracture subjects affected / exposed occurrences (all)	0 / 206 (0.00%) 0	1 / 197 (0.51%) 1	
Ligament sprain subjects affected / exposed occurrences (all)	1 / 206 (0.49%) 1	0 / 197 (0.00%) 0	
Stab wound subjects affected / exposed occurrences (all)	0 / 206 (0.00%) 0	1 / 197 (0.51%) 1	
Tendon rupture subjects affected / exposed occurrences (all)	0 / 206 (0.00%) 0	1 / 197 (0.51%) 1	
Cardiac disorders			
Palpitations subjects affected / exposed occurrences (all)	3 / 206 (1.46%) 3	0 / 197 (0.00%) 0	
Angina pectoris subjects affected / exposed occurrences (all)	1 / 206 (0.49%) 2	0 / 197 (0.00%) 0	
Nervous system disorders			

Dizziness		
subjects affected / exposed	7 / 206 (3.40%)	3 / 197 (1.52%)
occurrences (all)	7	3
Somnolence		
subjects affected / exposed	6 / 206 (2.91%)	1 / 197 (0.51%)
occurrences (all)	7	1
Headache		
subjects affected / exposed	4 / 206 (1.94%)	2 / 197 (1.02%)
occurrences (all)	5	3
Taste disorder		
subjects affected / exposed	2 / 206 (0.97%)	0 / 197 (0.00%)
occurrences (all)	2	0
Lumbosacral radiculopathy		
subjects affected / exposed	0 / 206 (0.00%)	1 / 197 (0.51%)
occurrences (all)	1	2
Balance disorder		
subjects affected / exposed	1 / 206 (0.49%)	0 / 197 (0.00%)
occurrences (all)	1	0
Migraine		
subjects affected / exposed	0 / 206 (0.00%)	1 / 197 (0.51%)
occurrences (all)	0	1
Paraesthesia		
subjects affected / exposed	1 / 206 (0.49%)	0 / 197 (0.00%)
occurrences (all)	1	0
Poor quality sleep		
subjects affected / exposed	1 / 206 (0.49%)	0 / 197 (0.00%)
occurrences (all)	1	0
Radicular pain		
subjects affected / exposed	1 / 206 (0.49%)	0 / 197 (0.00%)
occurrences (all)	1	0
Radiculopathy		
subjects affected / exposed	0 / 206 (0.00%)	1 / 197 (0.51%)
occurrences (all)	0	1
Tremor		
subjects affected / exposed	1 / 206 (0.49%)	0 / 197 (0.00%)
occurrences (all)	1	0

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 206 (0.49%)	0 / 197 (0.00%)	
occurrences (all)	1	0	
Leukopenia			
subjects affected / exposed	1 / 206 (0.49%)	0 / 197 (0.00%)	
occurrences (all)	1	0	
Thrombocytopenia			
subjects affected / exposed	0 / 206 (0.00%)	1 / 197 (0.51%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 206 (0.49%)	2 / 197 (1.02%)	
occurrences (all)	1	2	
Tinnitus			
subjects affected / exposed	0 / 206 (0.00%)	1 / 197 (0.51%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	15 / 206 (7.28%)	5 / 197 (2.54%)	
occurrences (all)	16	5	
Nausea			
subjects affected / exposed	8 / 206 (3.88%)	4 / 197 (2.03%)	
occurrences (all)	8	5	
Abdominal pain			
subjects affected / exposed	4 / 206 (1.94%)	0 / 197 (0.00%)	
occurrences (all)	4	0	
Frequent bowel movements			
subjects affected / exposed	4 / 206 (1.94%)	0 / 197 (0.00%)	
occurrences (all)	4	0	
Abdominal pain upper			
subjects affected / exposed	1 / 206 (0.49%)	2 / 197 (1.02%)	
occurrences (all)	1	2	
Flatulence			
subjects affected / exposed	0 / 206 (0.00%)	3 / 197 (1.52%)	
occurrences (all)	0	3	
Constipation			

subjects affected / exposed	2 / 206 (0.97%)	1 / 197 (0.51%)	
occurrences (all)	2	1	
Dyspepsia			
subjects affected / exposed	1 / 206 (0.49%)	1 / 197 (0.51%)	
occurrences (all)	2	1	
Gastrointestinal disorder			
subjects affected / exposed	1 / 206 (0.49%)	0 / 197 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal hypermotility			
subjects affected / exposed	0 / 206 (0.00%)	1 / 197 (0.51%)	
occurrences (all)	0	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 206 (0.00%)	1 / 197 (0.51%)	
occurrences (all)	0	1	
Teething			
subjects affected / exposed	1 / 206 (0.49%)	0 / 197 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	1 / 206 (0.49%)	0 / 197 (0.00%)	
occurrences (all)	1	0	
Hepatobiliary disorders			
Liver disorder			
subjects affected / exposed	0 / 206 (0.00%)	1 / 197 (0.51%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 206 (0.00%)	3 / 197 (1.52%)	
occurrences (all)	0	3	
Hyperhidrosis			
subjects affected / exposed	1 / 206 (0.49%)	1 / 197 (0.51%)	
occurrences (all)	1	1	
Pruritus			
subjects affected / exposed	1 / 206 (0.49%)	0 / 197 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			

Pollakiuria			
subjects affected / exposed	3 / 206 (1.46%)	0 / 197 (0.00%)	
occurrences (all)	3	0	
Dysuria			
subjects affected / exposed	0 / 206 (0.00%)	1 / 197 (0.51%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	9 / 206 (4.37%)	5 / 197 (2.54%)	
occurrences (all)	9	7	
Arthralgia			
subjects affected / exposed	1 / 206 (0.49%)	4 / 197 (2.03%)	
occurrences (all)	1	4	
Spinal pain			
subjects affected / exposed	0 / 206 (0.00%)	2 / 197 (1.02%)	
occurrences (all)	0	2	
Muscle spasms			
subjects affected / exposed	1 / 206 (0.49%)	0 / 197 (0.00%)	
occurrences (all)	1	0	
Muscular weakness			
subjects affected / exposed	0 / 206 (0.00%)	1 / 197 (0.51%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	0 / 206 (0.00%)	1 / 197 (0.51%)	
occurrences (all)	0	1	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 206 (0.97%)	3 / 197 (1.52%)	
occurrences (all)	3	3	
COVID-19			
subjects affected / exposed	1 / 206 (0.49%)	3 / 197 (1.52%)	
occurrences (all)	1	3	
Respiratory tract infection			
subjects affected / exposed	1 / 206 (0.49%)	1 / 197 (0.51%)	
occurrences (all)	1	1	
Urinary tract infection			

subjects affected / exposed	1 / 206 (0.49%)	1 / 197 (0.51%)	
occurrences (all)	1	1	
Viral infection			
subjects affected / exposed	2 / 206 (0.97%)	0 / 197 (0.00%)	
occurrences (all)	2	0	
Coronavirus infection			
subjects affected / exposed	0 / 206 (0.00%)	1 / 197 (0.51%)	
occurrences (all)	0	1	
Cystitis			
subjects affected / exposed	1 / 206 (0.49%)	0 / 197 (0.00%)	
occurrences (all)	1	0	
Enterovirus infection			
subjects affected / exposed	1 / 206 (0.49%)	0 / 197 (0.00%)	
occurrences (all)	1	0	
Laryngitis			
subjects affected / exposed	1 / 206 (0.49%)	0 / 197 (0.00%)	
occurrences (all)	1	0	
Periodontitis			
subjects affected / exposed	0 / 206 (0.00%)	1 / 197 (0.51%)	
occurrences (all)	0	1	
Pharyngitis			
subjects affected / exposed	0 / 206 (0.00%)	1 / 197 (0.51%)	
occurrences (all)	0	1	
Pneumonia			
subjects affected / exposed	1 / 206 (0.49%)	0 / 197 (0.00%)	
occurrences (all)	1	0	
Pulpitis dental			
subjects affected / exposed	0 / 206 (0.00%)	1 / 197 (0.51%)	
occurrences (all)	0	1	
Viral diarrhoea			
subjects affected / exposed	0 / 206 (0.00%)	1 / 197 (0.51%)	
occurrences (all)	0	1	
Respiratory tract infection viral			
subjects affected / exposed	0 / 206 (0.00%)	1 / 197 (0.51%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			

Increased appetite subjects affected / exposed occurrences (all)	1 / 206 (0.49%) 1	1 / 197 (0.51%) 1	
Decreased appetite subjects affected / exposed occurrences (all)	0 / 206 (0.00%) 0	1 / 197 (0.51%) 1	
Glucose tolerance impaired subjects affected / exposed occurrences (all)	0 / 206 (0.00%) 0	1 / 197 (0.51%) 1	
Hyperglycaemia subjects affected / exposed occurrences (all)	1 / 206 (0.49%) 1	0 / 197 (0.00%) 0	
Hyperlipidaemia subjects affected / exposed occurrences (all)	0 / 206 (0.00%) 0	1 / 197 (0.51%) 1	
Hypokalaemia subjects affected / exposed occurrences (all)	0 / 206 (0.00%) 0	1 / 197 (0.51%) 1	
Type 2 diabetes mellitus subjects affected / exposed occurrences (all)	0 / 206 (0.00%) 0	1 / 197 (0.51%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 June 2020	Substantial amendment to address CA comments to original protocol.
15 April 2021	To add new countries. To revise statistical power.
22 September 2022	To incorporate interim analysis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported