Clinical trial results:
A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Sialic Acid Extended-Release Tablets in Patients with GNE Myopathy (GNEM) or Hereditary Inclusion Body Myopathy (HIBM)

Summary

EudraCT number	2014-005432-33
Trial protocol	BG IT
Global end of trial date	09 June 2017

Results information

Result version number	v1 (current)
This version publication date	23 June 2018
First version publication date	23 June 2018

Trial information

Trial identification

Sponsor protocol code	UX001-CL301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02377921
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ultragenyx Pharmaceutical Inc.
Sponsor organisation address	60 Leveroni Court, Novato, California, United States, 94949
Public contact	Kim Mooney, Ultragenyx Pharmaceutical Inc., 415 4838813, kmooney@ultragenyx.com
Scientific contact	Medical Director, Ultragenyx Pharmaceutical Inc., 415 4838800,

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	09 June 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 June 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Evaluate the effect of 6 g/day SA-ER treatment of subjects with GNEM on upper extremity muscle strength (UEC score) as measured by dynamometry

Protection of trial subjects:

The trial was designed, conducted, recorded, and reported in accordance with the principles established by the 18th World Medical Association General Assembly (Helsinki, 1964) and subsequent amendments and clarifications adopted by the General Assemblies. The investigators made every effort to ensure that the study was conducted in full conformance with Helsinki principles, International Council for Harmonization (ICH) Good Clinical Practice (GCP) guidelines, current Food and Drug Administration (FDA) regulations, EU Clinical Trial Directive 2001/20/EC, and local ethical and regulatory requirements. Each investigator was thoroughly familiar with the appropriate administration and potential risks of administration of the study drug, as described in the protocol and Investigator's Brochure, prior to the initiation of the study. The method of obtaining and documenting informed consent and the contents of the informed consent form (ICF) complied with ICH GCP guidelines, the requirements of 21 CFR Part 50, "Protection of Human Subjects," the Health Insurance Portability and Accountability Act regulations, and all other applicable regulatory requirements. Investigators were responsible for preparing the ICF and submitting it to the Sponsor for approval prior to submission to the Institutional Review Board (IRB). All ICFs were written in regional language and contained the minimum elements for consent as mandated by the ICH guidelines. An IRB-approved ICF was provided by the Sponsor prior to initiation of the study. Investigators obtained signed written informed consent from each potential study subject prior to the conduct of any study procedures and after the methods, objectives, requirements, and potential risks of the study were fully explained to each potential subject. Consent for participation could be withdrawn at any time for any reason by the subject.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 May 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 18
Country: Number of subjects enrolled	Bulgaria: 11
Country: Number of subjects enrolled	France: 10
Country: Number of subjects enrolled	Israel: 9
Country: Number of subjects enrolled	Canada: 8
Country: Number of subjects enrolled	Italy: 11
Country: Number of subjects enrolled	United States: 22

Worldwide total number of subjects	89
EEA total number of subjects	50

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)	89
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The date of the Screening Visit was the date the subject signed informed consent for this study. The Baseline (Week 0) visit took place within 7 to 28 days of the Screening visit; subjects were randomized only after inclusion/exclusion criteria were confirmed.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Study parameters to achieve and maintain the double-blind status of the study included: sequential assignment of subject numbers; management of subject treatment assignment via an interactive web-based response system; labeling of study drug with the study number and a unique kit number; packaging and delivery of study drug supplies to sites in a manner that maintains blinding of site personnel; matched appearance of investigational product and placebo.

Arms

Are arms mutually exclusive?	Yes
Arm title	Ace-ER 6 g/Day

Arm description:

Aceneuramic acid extended-release (Ace-ER) 6 g/day, divided 3 times per day (TID) for 48 weeks.

Arm type	Experimental
Investigational medicinal product name	sialic acid (INN: aceneuramic acid)
Investigational medicinal product code	UX001
Other name	sialic acid extended-release (SA-ER)
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The 6000 mg (6 g) total daily SA dose was administered by the oral route and was divided into a TID regimen: 4 tablets taken in the morning, early evening, and before bedtime (qHS). The dose was to be administered with food (i.e. within 30 minutes of a meal or snack).

Arm title	Placebo

Arm description:

Matching placebo TID for 48 weeks.

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:

The placebo daily dose was given orally TID as 4 tablets taken in the morning, early evening, and qHS. The dose was to be administered with food (i.e. within 30 minutes of a meal or snack).

Number of subjects in period 1	Ace-ER 6 g/Day	Placebo
Started	45	44
Completed	44	43
Not completed	1	1
Subject non-compliance	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Ace-ER 6 g/Day
Reporting group description:	
Aceneuramic acid extended-release (Ace-ER) 6 g/day, divided 3 times per day (TID) for 48 weeks.	
Reporting group title	Placebo
Reporting group description:	
Matching placebo TID for 48 weeks.	

Reporting group values	Ace-ER 6 g/Day	Placebo	Total
Number of subjects	45	44	89
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	33.8	36.5	
standard deviation	± 7.91	± 8.65	-
Gender categorical Units: Subjects			
Female	20	20	40
Male	25	24	49
Ethnicity Units: Subjects			
Hispanic or Latino	5	7	12
Not Hispanic or Latino	39	34	73
Unknown or Not Reported	1	3	4
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	6	7	13
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	36	33	69
More than one race	0	0	0
Unknown or Not Reported	3	4	7
Upper Extremity Composite (UEC) Score			
Muscle strength based on the maximum voluntary isometric contraction (MVIC) against a dynamometer was measured bilaterally in the following upper extremity muscle groups: gross grip, shoulder abductors, elbow flexors, and elbow extensors. The UEC is derived from the sum of the average of the right and left total force values (measured in kg). Primary Analysis Set: subjects in the Ace-ER and placebo arms who had a Baseline and at least 1 postbaseline measurement (n=45, 43, respectively).			
Units: kg			
arithmetic mean	55.99	56.31	
standard deviation	± 26.950	± 29.287	-
Muscle Strength in the Knee Extensors			
Lower extremity muscle strength in the knee extensors was measured by dynamometry. Bilateral total			

force was defined as the average of the right and left force values (measured in kg). Primary Analysis Set: subjects in the Ace-ER and placebo arms who had a Baseline and at least 1 postbaseline measurement (n=45, 43, respectively).			
Units: kg			
arithmetic mean	26.53	26.65	
standard deviation	± 9.035	± 8.969	-
Lower Extremity Composite (LEC) Score			
Muscle strength based on MVIC against a dynamometer was measured bilaterally in the following lower extremity muscle groups: knee flexors, hip flexors, hip extensors, hip abductors and hip adductors. The LEC is derived from the sum of the average of the right and left total force values (measured in kg). Primary Analysis Set: subjects in the Ace-ER and placebo arms who had a Baseline and at least 1 postbaseline measurement (n=45, 43, respectively).			
Units: kg			
arithmetic mean	53.52	55.17	
standard deviation	± 33.751	± 39.324	-
Stands in Sit-to- Stand Test			
Lower extremity function was assessed using a sit-to-stand test. The number of times the subject can rise from a seated to a standing position in a 30-second period was recorded. Primary Analysis Set: subjects in the Ace-ER and placebo arms who had a Baseline and at least 1 postbaseline measurement (n=45, 43, respectively).			
Units: stands			
arithmetic mean	12.38	12.58	
standard deviation	± 4.103	± 4.316	-
Lifts in Weighted Arm Lift Test			
Upper extremity function was assessed using a weighted arm lift test performed bilaterally. The number of times the subject can raise a 1 kg weight above the head in a 30-second period was recorded. Primary Analysis Set: subjects in the Ace-ER and placebo arms who had a Baseline and at least 1 postbaseline measurement (n=45, 43, respectively).			
Units: arm lifts			
arithmetic mean	30.50	28.18	
standard deviation	± 10.452	± 9.824	-
Glucosamine (UDP-N-acetyl)-2-epimerase Myopathy Functional Activities Scale(GNEM-FAS)Mobility Score			
Lower extremity use and function was assessed using the Mobility domain of the GNEM-FAS instrument a disease specific measure developed to assess the functional impact of changes in muscle strength on mobility (reflective of the lower extremities). Mobility subscale scores range from 0 to 40 with higher scores representing greater mobility. Primary Analysis Set: subjects in the Ace-ER and placebo arms who had a Baseline and at least 1 postbaseline measurement (n=45, 43, respectively).			
Units: units on a scale			
arithmetic mean	26.38	26.23	
standard deviation	± 7.581	± 6.403	-
Distance Walked in 6-Minute Walk Test (6MWT)			
The total distance walked (meters) in a 6-minute period was measured. Primary Analysis Set: subjects in the Ace-ER and placebo arms who had a Baseline and at least 1 postbaseline measurement (n=45, 43, respectively).			
Units: meters			
arithmetic mean	367.0	361.2	
standard deviation	± 115.07	± 109.87	-
Percent of Predicted Distance Walked in			

6MWT			
The total distance walked (meters) in a 6-minute period was measured, and the percent predicted distance based on normative data for age and gender was estimated. Predicted Six-Minute Walk Test Distance (meters) = 868.8 - (2.99 x Age) - (74.7 x Sex), where Age is baseline age in years, and Sex = 0 for males, and 1 for females. Primary Analysis Set: subjects in the Ace-ER and placebo arms who had a Baseline and at least 1 postbaseline measurement (n=45, 43, respectively).			
Units: percentage of predicted meters			
arithmetic mean	49.97	49.87	
standard deviation	± 15.521	± 14.823	-

End points

End points reporting groups

Reporting group title	Ace-ER 6 g/Day
Reporting group description:	
Aceneuramic acid extended-release (Ace-ER) 6 g/day, divided 3 times per day (TID) for 48 weeks.	
Reporting group title	Placebo
Reporting group description:	
Matching placebo TID for 48 weeks.	
Subject analysis set title	Primary Analysis Set: Ace-ER 6 g/day
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects in the Ace-ER 6 g/day arm who had a Baseline and at least 1 postbaseline measurement.	
Subject analysis set title	Primary Analysis Set: Placebo
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects in the placebo arm who had a Baseline and at least 1 postbaseline measurement.	

Primary: Change From Baseline in UEC Score (Total Force in kg) at Week 48

End point title	Change From Baseline in UEC Score (Total Force in kg) at Week 48
End point description:	
Muscle strength based on the MVIC against a dynamometer was measured bilaterally in the following upper extremity muscle groups: gross grip, shoulder abductors, elbow flexors, and elbow extensors. The UEC is derived from the sum of the average of the right and left total force values (measured in kg).	
End point type	Primary
End point timeframe:	
Baseline, Week 48	

End point values	Primary Analysis Set: Ace-ER 6 g/day	Primary Analysis Set: Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	45	43		
Units: kg				
least squares mean (confidence interval 95%)	-2.25 (-3.77 to -0.74)	-2.99 (-4.69 to -1.28)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Primary Analysis Set: Ace-ER 6 g/day v Primary Analysis Set: Placebo

Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5387 [1]
Method	GEE model
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.61
upper limit	3.09

Notes:

[1] - Generalized estimating equation (GEE) model includes change from Baseline (BL) as dependent variable, visit, treatment and visit by treatment as fixed factors, and BL values, sex, and region as covariates, with compound symmetry covariance structure.

Secondary: Change From Baseline in Muscle Strength in the Knee Extensors at Week 48

End point title	Change From Baseline in Muscle Strength in the Knee Extensors at Week 48

End point description:

Lower extremity muscle strength in the knee extensors was measured by dynamometry. Bilateral total force was defined as the average of the right and left force values (measured in kg).

End point type	Secondary

End point timeframe:

Baseline, Week 48

End point values	Primary Analysis Set: Ace-ER 6 g/day	Primary Analysis Set: Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	45	43		
Units: kg				
least squares mean (confidence interval 95%)	0.05 (-1.19 to 1.29)	0.45 (-1.20 to 2.10)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Primary Analysis Set: Placebo v Primary Analysis Set: Ace-ER 6 g/day
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6938 [2]
Method	GEE model
Parameter estimate	LS Mean Difference
Point estimate	-0.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.38
upper limit	1.58

Notes:

[2] - GEE model includes change from Baseline as dependent variable, visit, treatment and visit by treatment as fixed factors, and Baseline values, sex, and region as covariates, with compound symmetry covariance structure.

Secondary: Change From Baseline in LEC Score (Total Force in kg) at Week 48

End point title	Change From Baseline in LEC Score (Total Force in kg) at Week 48

End point description:

Muscle strength based on MVIC against a dynamometer was measured bilaterally in the following lower extremity muscle groups: knee flexors, hip flexors, hip extensors, hip abductors and hip adductors. The LEC is derived from the sum of the average of the right and left total force values (measured in kg).

End point type	Secondary

End point timeframe:

Baseline, Week 48

End point values	Primary Analysis Set: Ace-ER 6 g/day	Primary Analysis Set: Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	45	43		
Units: kg				
least squares mean (confidence interval 95%)	-1.92 (-4.49 to 0.65)	-0.44 (-3.96 to 3.09)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Primary Analysis Set: Placebo v Primary Analysis Set: Ace-ER 6 g/day
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5023 [3]
Method	GEE model
Parameter estimate	LS Mean Difference
Point estimate	-1.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.83
upper limit	2.86

Notes:

[3] - GEE model includes change from Baseline as dependent variable, visit, treatment and visit by treatment as fixed factors, and Baseline values, sex, and region as covariates, with compound symmetry covariance structure.

Secondary: Change From Baseline in GNEM FAS Mobility Domain Score at Week 48

End point title	Change From Baseline in GNEM FAS Mobility Domain Score at Week 48

End point description:

Lower extremity use and function was assessed using the Mobility domain of the GNEM-FAS instrument a disease specific measure developed to assess the functional impact of changes in muscle strength on mobility (reflective of the lower extremities). Mobility subscale scores range from 0 to 40 with higher scores representing greater mobility.

End point type	Secondary

End point timeframe:

Baseline, Week 48

End point values	Primary Analysis Set: Ace-ER 6 g/day	Primary Analysis Set: Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	45	43		
Units: units on a scale				
least squares mean (confidence interval 95%)	-2.49 (-3.56 to -1.42)	-1.77 (-2.59 to -0.95)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Primary Analysis Set: Ace-ER 6 g/day v Primary Analysis Set: Placebo
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2739 [4]
Method	GEE model
Parameter estimate	LS Mean Difference
Point estimate	-0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.01
upper limit	0.57

Notes:

[4] - GEE model includes change from Baseline as dependent variable, visit, treatment and visit by treatment as fixed factors, and Baseline values, sex, and region as covariates, with compound symmetry covariance structure.

Secondary: Change From Baseline in Number of Lifts in the 30 Second Weighted Arm Lift Test at Week 48

End point title	Change From Baseline in Number of Lifts in the 30 Second

	Weighted Arm Lift Test at Week 48

End point description:

Upper extremity function was assessed using a weighted arm lift test performed bilaterally. The number of times the subject can raise a 1 kg weight above the head in a 30-second period was recorded.

End point type	Secondary

End point timeframe:

Baseline, Week 48

End point values	Primary Analysis Set: Ace-ER 6 g/day	Primary Analysis Set: Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	45	43		
Units: arm lifts				
least squares mean (confidence interval 95%)	0.03 (-2.19 to 2.26)	2.79 (0.21 to 5.38)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Primary Analysis Set: Ace-ER 6 g/day v Primary Analysis Set: Placebo
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1235 [5]
Method	GEE model
Parameter estimate	LS Mean Difference
Point estimate	-2.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.27
upper limit	0.75

Notes:

[5] - GEE model includes change from Baseline as dependent variable, visit, treatment and visit by treatment as fixed factors, and Baseline values, sex, and region as covariates, with compound symmetry covariance structure.

Secondary: Change From Baseline in Number of Stands in the Sit to Stand Test at Week 48

End point title	Change From Baseline in Number of Stands in the Sit to Stand Test at Week 48

End point description:

Lower extremity function was assessed using a sit-to-stand test. The number of times the participant can rise from a seated to a standing position in a 30-second period was recorded.

End point type	Secondary

End point timeframe:

Baseline, Week 48

End point values	Primary Analysis Set: Ace-ER 6 g/day	Primary Analysis Set: Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	45	43		
Units: stands				
least squares mean (confidence interval 95%)	0.11 (-0.55 to 0.77)	0.53 (-0.21 to 1.28)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Primary Analysis Set: Ace-ER 6 g/day v Primary Analysis Set: Placebo
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3907 [6]
Method	GEE model
Parameter estimate	LS Mean Difference
Point estimate	-0.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	0.55

Notes:

[6] - GEE model includes change from Baseline as dependent variable, visit, treatment and visit by treatment as fixed factors, and Baseline values, sex, and region as covariates, with compound symmetry covariance structure.

Secondary: Change From Baseline in Meters Walked in the 6MWT at Week 48

End point title	Change From Baseline in Meters Walked in the 6MWT at Week 48
End point description:	
The total distance walked (meters) in a 6-minute period was measured.	
End point type	Secondary
End point timeframe:	
Baseline, Week 48	

End point values	Primary Analysis Set: Ace-ER 6 g/day	Primary Analysis Set: Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	45	43		
Units: meters				
least squares mean (confidence interval 95%)	-17.79 (-32.09 to -3.50)	-6.81 (-16.83 to 3.21)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Primary Analysis Set: Ace-ER 6 g/day v Primary Analysis Set: Placebo
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1964 [7]
Method	GEE model
Parameter estimate	LS Mean Difference
Point estimate	-10.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	-27.64
upper limit	5.68

Notes:

[7] - GEE model includes change from Baseline as dependent variable, visit, treatment and visit by treatment as fixed factors, and Baseline values, sex, and region as covariates, with compound symmetry covariance structure.

Secondary: Change From Baseline in Percent Predicted Meters Walked in the 6MWT at Week 48

End point title	Change From Baseline in Percent Predicted Meters Walked in the 6MWT at Week 48

End point description:

The total distance walked (meters) in a 6-minute period was measured, and the percent predicted distance based on normative data for age and gender was estimated.

End point type	Secondary

End point timeframe:

Baseline, Week 48

End point values	Primary Analysis Set: Ace-ER 6 g/day	Primary Analysis Set: Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	45	43		
Units: percentage of predicted meters				
least squares mean (confidence interval 95%)	-2.37 (-4.30 to -0.44)	-0.97 (-2.32 to 0.38)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Primary Analysis Set: Ace-ER 6 g/day v Primary Analysis Set: Placebo
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2241 [8]
Method	GEE model
Parameter estimate	LS Mean Difference
Point estimate	-1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.66
upper limit	0.86

Notes:

[8] - GEE model includes change from Baseline as dependent variable, visit, treatment and visit by treatment as fixed factors, and Baseline values, sex, and region as covariates, with compound symmetry covariance structure.

Secondary: Change From Baseline in GNEM FAS Upper Extremity Domain Score at Week 48

End point title	Change From Baseline in GNEM FAS Upper Extremity Domain Score at Week 48

End point description:

Upper extremity use and function was assessed using the Mobility domain of the GNEM-FAS instrument a disease specific measure developed to assess the functional impact of changes in muscle strength on mobility (reflective of the upper extremities). Mobility subscale scores range from 0 to 40 with higher scores representing greater mobility.

End point type	Secondary

End point timeframe:

Baseline, Week 48

End point values	Primary Analysis Set: Ace-ER 6 g/day	Primary Analysis Set: Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	45	43		
Units: units on a scale				
least squares mean (confidence interval 95%)	-1.40 (-2.21 to -0.58)	-1.08 (-1.86 to -0.29)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Primary Analysis Set: Ace-ER 6 g/day v Primary Analysis Set: Placebo
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5608 [9]
Method	GEE model
Parameter estimate	LS Mean Difference
Point estimate	-0.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.39
upper limit	0.75

Notes:

[9] - GEE model includes change from Baseline as dependent variable, visit, treatment and visit by treatment as fixed factors, and Baseline values, sex, and region as covariates, with compound symmetry covariance structure.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Screening through Week 48 plus 28 days (+5 days). The mean (SD) duration of treatment was 340.2 (12.02) days and 332.9 (40.86) days for the Ace-ER and placebo groups, respectively.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Ace-ER 6 g/day

Reporting group description:

PLACEHOLDER

Reporting group title	Placebo

Reporting group description:

PLACEHOLDER

Serious adverse events	Ace-ER 6 g/day	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 45 (4.44%)	1 / 44 (2.27%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 45 (2.22%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion			
subjects affected / exposed	0 / 45 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	1 / 45 (2.22%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Ace-ER 6 g/day	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 45 (84.44%)	30 / 44 (68.18%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	4 / 45 (8.89%)	2 / 44 (4.55%)	
occurrences (all)	5	3	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	7 / 45 (15.56%)	7 / 44 (15.91%)	
occurrences (all)	25	11	
Contusion			
subjects affected / exposed	4 / 45 (8.89%)	0 / 44 (0.00%)	
occurrences (all)	5	0	
Skin abrasion			
subjects affected / exposed	0 / 45 (0.00%)	3 / 44 (6.82%)	
occurrences (all)	0	3	
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 45 (6.67%)	1 / 44 (2.27%)	
occurrences (all)	3	1	
Dysgeusia			
subjects affected / exposed	3 / 45 (6.67%)	0 / 44 (0.00%)	
occurrences (all)	4	0	
Headache			
subjects affected / exposed	7 / 45 (15.56%)	7 / 44 (15.91%)	
occurrences (all)	10	8	
Sciatica			
subjects affected / exposed	0 / 45 (0.00%)	3 / 44 (6.82%)	
occurrences (all)	0	4	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 45 (4.44%)	3 / 44 (6.82%)	
occurrences (all)	2	3	

Fatigue			
subjects affected / exposed	4 / 45 (8.89%)	4 / 44 (9.09%)	
occurrences (all)	5	5	
Influenza like illness			
subjects affected / exposed	4 / 45 (8.89%)	11 / 44 (25.00%)	
occurrences (all)	4	12	
Pain			
subjects affected / exposed	1 / 45 (2.22%)	3 / 44 (6.82%)	
occurrences (all)	1	3	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	4 / 45 (8.89%)	4 / 44 (9.09%)	
occurrences (all)	4	4	
Abdominal pain upper			
subjects affected / exposed	10 / 45 (22.22%)	3 / 44 (6.82%)	
occurrences (all)	11	3	
Diarrhoea			
subjects affected / exposed	8 / 45 (17.78%)	6 / 44 (13.64%)	
occurrences (all)	11	8	
Flatulence			
subjects affected / exposed	6 / 45 (13.33%)	5 / 44 (11.36%)	
occurrences (all)	6	6	
Frequent bowel movements			
subjects affected / exposed	3 / 45 (6.67%)	0 / 44 (0.00%)	
occurrences (all)	3	0	
Nausea			
subjects affected / exposed	5 / 45 (11.11%)	2 / 44 (4.55%)	
occurrences (all)	7	3	
Respiratory, thoracic and mediastinal disorders			
Nasal congestion			
subjects affected / exposed	4 / 45 (8.89%)	1 / 44 (2.27%)	
occurrences (all)	4	1	
Cough			
subjects affected / exposed	5 / 45 (11.11%)	4 / 44 (9.09%)	
occurrences (all)	5	4	
Oropharyngeal pain			

subjects affected / exposed	4 / 45 (8.89%)	2 / 44 (4.55%)	
occurrences (all)	5	2	
Psychiatric disorders			
Sleep disorder			
subjects affected / exposed	0 / 45 (0.00%)	4 / 44 (9.09%)	
occurrences (all)	0	4	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	9 / 45 (20.00%)	5 / 44 (11.36%)	
occurrences (all)	13	5	
Muscular weakness			
subjects affected / exposed	6 / 45 (13.33%)	3 / 44 (6.82%)	
occurrences (all)	9	5	
Back pain			
subjects affected / exposed	5 / 45 (11.11%)	4 / 44 (9.09%)	
occurrences (all)	6	5	
Musculoskeletal pain			
subjects affected / exposed	4 / 45 (8.89%)	2 / 44 (4.55%)	
occurrences (all)	5	3	
Myalgia			
subjects affected / exposed	6 / 45 (13.33%)	1 / 44 (2.27%)	
occurrences (all)	6	1	
Pain in extremity			
subjects affected / exposed	4 / 45 (8.89%)	3 / 44 (6.82%)	
occurrences (all)	5	4	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	5 / 45 (11.11%)	1 / 44 (2.27%)	
occurrences (all)	6	1	
Influenza			
subjects affected / exposed	1 / 45 (2.22%)	4 / 44 (9.09%)	
occurrences (all)	3	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 March 2015	1. Inclusion Criterion was updated to state that participants of childbearing potential or with partners of child-bearing potential must consent to use a highly effective method of contraception. The abstinence language was also updated. 2. Stopping Rules were updated to state that Regulatory Authorities, as well as IRBs and ethics committees (ECs), would be informed should unexpected and possibly, probably, or definitely drug-related serious adverse events (SAEs) occurred and/or if the study was paused or stopped per recommendation from the data monitoring committee (DMC). Language was also added stating that, if paused or stopped, the trial would only be restarted following approval by Regulatory Authorities. 3. Updated to include language that if emergent suicidal ideation or behavior was indicated upon review of the Columbia-Suicide Severity Rating Scale (C-SSRS), the investigator should promptly evaluate the subject to ensure proper management and protection of subject safety. 4. Multiple sections were updated to define the Sponsor's responsibilities with regard to reporting SAEs/Suspected Unexpected Serious Adverse Reactions (SUSARs).
23 September 2015	1. Inclusion Criterion was updated to increase the upper age limit from 50 to 55. 2. Updated to clarify that leftover biological samples (from the protocol specified blood and urine requirements) may be used for future research including, but not limited to, biomarker research.
25 March 2016	1. Synopsis, Data Monitoring Committee, and Review of Safety Data were updated to indicate that DMC meetings would occur at least 2 times per year instead of quarterly. 2. Schedule of Events was updated to remove the free, total and bound urine SA levels from the Screening Visit. Drug Concentrations Measurements was also updated to reflect this change. 3. Schedule of Events, Footnote g was updated to clarify how the urine sample for N-acetyl-D-mannosamine (ManNAc) testing would be collected. Urine Testing for ManNAc was also updated to reflect this change. 4. Schedule of Events and Selection of Doses and Study Duration were updated to reflect that the Safety Follow up Visit was to be conducted by phone, including clarifications around the Safety Follow-up Call. Based on this change, the assessments to be conducted at this visit were updated to indicate that the Safety Follow-up Call was only for subjects who completed the study and chose not to enroll in the extension study, UX001-CL302, or who discontinued the study early. This call was not required for subjects who were eligible and chose to take part in the extension study, UX001-CL302. Information on any ongoing or new AEs, SAEs, and concomitant medications was to be collected in this phone call. 5. Discussion of Study Design, Including Choice of Control Group was updated to include additional rationale for the 6WMT as a secondary endpoint. 6. List of Abbreviations and Definition of Terms was updated to include "TC", defined as telephone call. 7. Removal of Subjects from Therapy or Assessment, Adverse Events, Adverse Event Reporting, General, Serious Adverse Events, Serious Adverse Drug Reactions, and Requirements for Immediate Reporting, Adverse Drug Reaction Reporting, and Urgent Safety Measures were updated to clarify the end of the data collection period for safety reporting events based on the change to the Safety Follow-up Call (refer to Summary of Change #4 above).

25 March 2016	(continued) 8. Study Schedule was updated based on the change to the Safety Follow up Call (refer to Summary of Change #4 above) and to clarify that Screening procedures may have taken place across multiple days to allow enough time to complete all procedures and confirm initial subject eligibility. 9. Dynamometry was updated to clarify the number of test attempts that would be administered for each muscle group (3 versus up to 3). For data analysis, the highest value (rather than an average of the 3 values) was still utilized as specified in the original protocol. 10. Dynamometry was updated to remove an outdated reference for normative grip strength data. 11. Six Minute Walk Test was updated to clarify the 6MWT administration for this protocol. 12. Table and Clinical Laboratory Tests for Safety were updated to clarify the analytes that would be tested in the urinalysis (added blood and leukocyte esterase) and to clarify that microscopic evaluation would be conducted for abnormal urine test results. 13. Volume of Blood to Be Drawn from Each Subject and associated Table were updated to clarify the volume of blood that would be drawn for the serum SA tests, to reduce the number of chemistry and hematology samples obtained, and to clarify the overall volume of blood that would be obtained during the study. The total mL of blood collected through study completion was increased from 108.5 mL to 119.0 mL. 14. Individual Neuromuscular Quality of Life Questionnaire was updated to provide guidance on administering the test to subjects when the scale was not available in the subject's native language. 15. Pregnancy Testing was updated to remove the reference to a pregnancy test at the Safety Follow-up Visit. 16. Populations Analyzed was updated to match the definition of the SA Analysis Set between the synopsis and the protocol body (ie, urine SA levels was added to Section).
25 March 2016	(continued) 17. Subject Information and Consent was modified to remove the requirement for assent from subjects under the age of 18. 18. Safety Contact Information was updated with the correct email address for the Medical Monitor. 19. References section was updated to remove the outdated normative grip strength data reference.
25 May 2017	1. The study objectives were modified to designate 3 secondary objectives as "key" secondary objectives. These 3 secondary objectives were to evaluate the effect of 6 g/day of Ace-ER treatment of subjects with GNEM on the following: - Lower extremity composite muscle strength score as measured by dynamometry - Muscle strength in the knee extensors as measured by dynamometry - Physical functioning as measured using the GNEM-FAS mobility domain score 2. Three secondary clinical efficacy endpoints were designated as "key" secondary endpoints. These included the following: - LEC score based on a sum of the mean bilateral strength recorded in the following muscle groups: knee flexors, hip flexors, hip extensors, hip abductors, and hip adductors - Muscle strength in the knee extensors: bilateral total force (in kg) - GNEM FAS mobility domain score Percent predicted muscle strength in the knee extensors was previously included as a secondary endpoint (in addition to total force) and was now listed separately as a tertiary endpoint. 3. Text was added to indicate that Hochberg's adjustment for multiplicity would be applied for the 3 key secondary endpoints. In addition, geographic region and sex were added as covariates for the primary efficacy analysis. 4. Language regarding urinary SA as a tertiary objective and its assessment was modified. Urinary SA was measured but was not used as a determination of Ace-ER absorption, excretion, and pharmacodynamics.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported