Clinical trial results:
A Phase 3b Open-label Extension Study to Evaluate the Safety and Efficacy of Aceneuramic Acid Extended-Release (Ace-ER) Tablets in Patients with GNE Myopathy (GNEM) or Hereditary Inclusion Body Myopathy (HIBM)

Summary

EudraCT number	2016-000360-42
Trial protocol	GB BG IT
Global end of trial date	10 January 2018

Results information

Result version number	v2 (current)
This version publication date	28 March 2019
First version publication date	23 January 2019
Version creation reason	• New data added to full data set Correction of unit of measure

Trial information

Trial identification

Sponsor protocol code	UX001-CL302

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02736188
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ultragenyx Pharmaceutical Inc.
Sponsor organisation address	60 Leveroni Court, Novato, United States, California 94949
Public contact	Medical Information, Ultragenyx Pharmaceutical Inc., 1 888-756-8657, medinfo@ultragenyx.com
Scientific contact	Medical Information, Ultragenyx Pharmaceutical Inc., 1 888-756-8657, medinfo@ultragenyx.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	10 January 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 January 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The objective of this study is to evaluate the long-term safety and efficacy of Ace-ER treatment in subjects with glucosamine (UDP-N-acetyl)-2-epimerase myopathy (GNEM).

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	02 May 2016
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	United States: 55
Country: Number of subjects enrolled	United Kingdom: 18
Country: Number of subjects enrolled	Bulgaria: 10
Country: Number of subjects enrolled	France: 10
Country: Number of subjects enrolled	Italy: 11
Country: Number of subjects enrolled	Israel: 30
Country: Number of subjects enrolled	Canada: 9

Worldwide total number of subjects	143
EEA total number of subjects	49

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)	141
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

143 subjects were screened and enrolled across 14 total sites in the United States, Israel, United Kingdom, Italy, France, Canada, and Bulgaria. 87 subjects rolled over from study UX001-CL301 (NCT02377921), 49 subjects rolled over from study UX001-CL202 (NCT01830972), and 7 subjects rolled over from UX001-CL203 (NCT02731690).

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	143
Number of subjects completed	142

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Withdrew consent prior to receiving first dose: 1

Period 1

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

Arms

Arm title	Ace-ER 6 g/Day

Arm description:

4 tablets (500 mg Ace-ER each for 2 g per dose) orally 3 times per day

Arm type	Experimental
Investigational medicinal product name	Aceneuramic Acid Extended-Release Tablets
Investigational medicinal product code	UX001
Other name	Sialic Acid Extended Release, Ace-ER
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Dose was taken with food (i.e. within 30 minutes after a meal or snack).

Number of subjects in period 1[1]	Ace-ER 6 g/Day
Started	142
Completed	0
Not completed	142
Adverse Event	1
Not Specified	6
Discontinuation of Study by Sponsor	134
Withdrawal by Subject	1

Notes:

[1] - 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: 1 subject withdrew consent prior to receiving the first dose and is accounted for in preassignment details.

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	142	142	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	74		
standard deviation	± 68	-	
Gender categorical Units: Subjects			
Female	74	74	
Male	68	68	
Ethnicity Units: Subjects			
Hispanic or Latino	14	14	
Not Hispanic or Latino	125	125	
Unknown or Not Reported	3	3	
Race Units: Subjects			
White	111	111	
Asian	19	19	
Other, Not Specified	12	12	
Hand Held Dynamometry (HHD) Upper Extremity Composite Score (UEC)			
Hand held dynamometry testing was used to measure strength. The maximum voluntary isometric contraction against a dynamometer was used to measure bilateral strength in the following muscle groups: shoulder abductors, wrist extensors and knee extensors. Specialized dynamometers for the measurement of grip and key pinch strength were also used. The total force (in kilogram-force [kgf]) for each was recorded.			
Units: kgf			
arithmetic mean			
standard deviation	±	-	
GNEM Functional Activities Scale (GNEM-FAS) Mobility Score			
GNEM-FAS Expanded Version Mobility subscale score has 13 items and ranges from 0 to 52 with higher scores representing greater mobility.			
Units: score on a scale			
arithmetic mean			
standard deviation	±	-	
GNEM-FAS Expanded Version Upper Extremity Score			
GNEM-FAS Expanded Version Upper Extremity subscale score has 9 items and ranges from 0 to 36 with higher scores representing more skilled, independent use of the arms during functional activity performance.			
Units: score on a scale			

arithmetic mean standard deviation	±	-	
HHD Lower Extremity Composite (LEC) Score			
Hand held dynamometry testing was used to measure strength. The maximum voluntary isometric contraction against a dynamometer was used to measure bilateral strength in the following muscle groups: shoulder abductors, wrist extensors and knee extensors. Specialized dynamometers for the measurement of grip and key pinch strength were also used. The total force (in kgf) for each was recorded. n=86 subjects in the Full Analysis Set with a baseline assessment for this measure			
Units: kgf arithmetic mean standard deviation	±	-	
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.			
Units: stands arithmetic mean standard deviation	±	-	
30-second 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. n=72 subjects in the Full Analysis Set with a baseline assessment for this measure			
Units: lifts arithmetic mean standard deviation	±	-	
Six-Minute Walk Test (6MWT)			
The total distance walked (meters) in a 6-minute period was measured. n=83 subjects in the Full Analysis Set with a baseline assessment for this measure			
Units: meters arithmetic mean standard deviation	±	-	
Percent Predicted Meters 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 6MWT 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. n=83 subjects in the Full Analysis Set with a baseline assessment for this measure			
Units: percentage of predicted meters arithmetic mean standard deviation	±	-	
Total Force in Knee Extensors			
Hand held dynamometry testing was used to measure strength. The maximum voluntary isometric contraction against a dynamometer was used to measure bilateral strength in the following muscle groups: shoulder abductors, wrist extensors and knee extensors. Specialized dynamometers for the measurement of grip and key pinch strength were also used. The total force (in kgf) for each was recorded. n=84 subjects in the Full Analysis Set with a baseline assessment for this measure			
Units: kgf arithmetic mean standard deviation	±	-	
Percent of Predicted Total Force in Knee Extensors			

The percent predicted total force value of lower extremity muscle strength in the knee extensors was determined based on reference equations adjusting for age, gender, height, and weight. n=81 subjects in the Full Analysis Set with a baseline assessment for this measure			
Units: percent of predicted total force arithmetic mean standard deviation	± 	- 	

Subject analysis sets

Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description: All subjects in parent study UX001-CL301 with a UX001-CL302 baseline measurement and at least one post-baseline measurement in UX001-CL302.	
Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis
Subject analysis set description: All subjects who received at least one dose of study drug in UX001-CL302.	
Subject analysis set title	Ace-ER 6 g/Day (Parent Study Treatment: Ace-ER 6 g/Day)
Subject analysis set type	Full analysis
Subject analysis set description: 4 tablets (500 mg Ace-ER each for 2 g per dose) orally 3 times per day in subjects who took Ace-ER in study UX001-CL301	
Subject analysis set title	Ace-ER 6 g/Day (Parent Study Treatment: Placebo)
Subject analysis set type	Full analysis
Subject analysis set description: 4 tablets (500 mg Ace-ER each for 2 g per dose) orally 3 times per day in subjects who took placebo in study UX001-CL301	

Reporting group values	Full Analysis Set	Safety Analysis Set	Ace-ER 6 g/Day (Parent Study Treatment: Ace-ER 6 g/Day)
Number of subjects	87	142	44
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 ±	 ±	 ±
Gender categorical Units: Subjects			
Female Male			
Ethnicity Units: Subjects			
Hispanic or Latino Not Hispanic or Latino Unknown or Not Reported			
Race Units: Subjects			
White			

Asian			
Other, Not Specified			

Hand Held Dynamometry (HHD) Upper Extremity Composite Score (UEC)			
Hand held dynamometry testing was used to measure strength. The maximum voluntary isometric contraction against a dynamometer was used to measure bilateral strength in the following muscle groups: shoulder abductors, wrist extensors and knee extensors. Specialized dynamometers for the measurement of grip and key pinch strength were also used. The total force (in kilogram-force [kgf]) for each was recorded.			
Units: kgf			
arithmetic mean	52.98		
standard deviation	± 28.814	±	±
GNEM Functional Activities Scale (GNEM-FAS) Mobility Score			
GNEM-FAS Expanded Version Mobility subscale score has 13 items and ranges from 0 to 52 with higher scores representing greater mobility.			
Units: score on a scale			
arithmetic mean	24.17		
standard deviation	± 7.772	±	±
GNEM-FAS Expanded Version Upper Extremity Score			
GNEM-FAS Expanded Version Upper Extremity subscale score has 9 items and ranges from 0 to 36 with higher scores representing more skilled, independent use of the arms during functional activity performance.			
Units: score on a scale			
arithmetic mean	27.53		
standard deviation	± 4.938	±	±
HHD Lower Extremity Composite (LEC) Score			
Hand held dynamometry testing was used to measure strength. The maximum voluntary isometric contraction against a dynamometer was used to measure bilateral strength in the following muscle groups: shoulder abductors, wrist extensors and knee extensors. Specialized dynamometers for the measurement of grip and key pinch strength were also used. The total force (in kgf) for each was recorded. n=86 subjects in the Full Analysis Set with a baseline assessment for this measure			
Units: kgf			
arithmetic mean	51.91		
standard deviation	± 37.474	±	±
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.			
Units: stands			
arithmetic mean	12.75		
standard deviation	± 4.977	±	±
30-second 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. n=72 subjects in the Full Analysis Set with a baseline assessment for this measure			
Units: lifts			
arithmetic mean	30.93		
standard deviation	± 13.171	±	±
Six-Minute Walk Test (6MWT)			
The total distance walked (meters) in a 6-minute period was measured. n=83 subjects in the Full Analysis Set with a baseline assessment for this measure			

Units: meters			
arithmetic mean	359.4		
standard deviation	± 123.94	±	±
Percent Predicted Meters 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 6MWT 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. n=83 subjects in the Full Analysis Set with a baseline assessment for this measure			
Units: percentage of predicted meters			
arithmetic mean	49.52		
standard deviation	± 16.962	±	±
Total Force in Knee Extensors			
Hand held dynamometry testing was used to measure strength. The maximum voluntary isometric contraction against a dynamometer was used to measure bilateral strength in the following muscle groups: shoulder abductors, wrist extensors and knee extensors. Specialized dynamometers for the measurement of grip and key pinch strength were also used. The total force (in kgf) for each was recorded. n=84 subjects in the Full Analysis Set with a baseline assessment for this measure			
Units: kgf			
arithmetic mean	26.60		
standard deviation	± 9.746	±	±
Percent of Predicted Total Force in Knee Extensors			
The percent predicted total force value of lower extremity muscle strength in the knee extensors was determined based on reference equations adjusting for age, gender, height, and weight. n=81 subjects in the Full Analysis Set with a baseline assessment for this measure			
Units: percent of predicted total force			
arithmetic mean	13.69		
standard deviation	± 15.323	±	±

Reporting group values	Ace-ER 6 g/Day (Parent Study Treatment: Placebo)		
Number of subjects	43		
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	±		
Gender categorical Units: Subjects			
Female			
Male			
Ethnicity Units: Subjects			
Hispanic or Latino			
Not Hispanic or Latino			
Unknown or Not Reported			
Race Units: Subjects			

White Asian Other, Not Specified			
Hand Held Dynamometry (HHD) Upper Extremity Composite Score (UEC)			
Hand held dynamometry testing was used to measure strength. The maximum voluntary isometric contraction against a dynamometer was used to measure bilateral strength in the following muscle groups: shoulder abductors, wrist extensors and knee extensors. Specialized dynamometers for the measurement of grip and key pinch strength were also used. The total force (in kilogram-force [kgf]) for each was recorded.			
Units: kgf arithmetic mean standard deviation	±		
GNEM Functional Activities Scale (GNEM-FAS) Mobility Score			
GNEM-FAS Expanded Version Mobility subscale score has 13 items and ranges from 0 to 52 with higher scores representing greater mobility.			
Units: score on a scale arithmetic mean standard deviation	±		
GNEM-FAS Expanded Version Upper Extremity Score			
GNEM-FAS Expanded Version Upper Extremity subscale score has 9 items and ranges from 0 to 36 with higher scores representing more skilled, independent use of the arms during functional activity performance.			
Units: score on a scale arithmetic mean standard deviation	±		
HHD Lower Extremity Composite (LEC) Score			
Hand held dynamometry testing was used to measure strength. The maximum voluntary isometric contraction against a dynamometer was used to measure bilateral strength in the following muscle groups: shoulder abductors, wrist extensors and knee extensors. Specialized dynamometers for the measurement of grip and key pinch strength were also used. The total force (in kgf) for each was recorded. n=86 subjects in the Full Analysis Set with a baseline assessment for this measure			
Units: kgf arithmetic mean standard deviation	±		
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.			
Units: stands arithmetic mean standard deviation	±		
30-second 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. n=72 subjects in the Full Analysis Set with a baseline assessment for this measure			
Units: lifts arithmetic mean standard deviation	±		
Six-Minute Walk Test (6MWT)			
The total distance walked (meters) in a 6-minute period was measured. n=83 subjects in the Full Analysis Set with a baseline assessment for this measure			

Units: meters arithmetic mean standard deviation	±		
Percent Predicted Meters 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 6MWT 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. n=83 subjects in the Full Analysis Set with a baseline assessment for this measure			
Units: percentage of predicted meters arithmetic mean standard deviation	±		
Total Force in Knee Extensors			
Hand held dynamometry testing was used to measure strength. The maximum voluntary isometric contraction against a dynamometer was used to measure bilateral strength in the following muscle groups: shoulder abductors, wrist extensors and knee extensors. Specialized dynamometers for the measurement of grip and key pinch strength were also used. The total force (in kgf) for each was recorded. n=84 subjects in the Full Analysis Set with a baseline assessment for this measure			
Units: kgf arithmetic mean standard deviation	±		
Percent of Predicted Total Force in Knee Extensors			
The percent predicted total force value of lower extremity muscle strength in the knee extensors was determined based on reference equations adjusting for age, gender, height, and weight. n=81 subjects in the Full Analysis Set with a baseline assessment for this measure			
Units: percent of predicted total force arithmetic mean standard deviation	±		

End points

End points reporting groups

Reporting group title	Ace-ER 6 g/Day
Reporting group description:	
4 tablets (500 mg Ace-ER each for 2 g per dose) orally 3 times per day	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
All subjects in parent study UX001-CL301 with a UX001-CL302 baseline measurement and at least one post-baseline measurement in UX001-CL302.	
Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects who received at least one dose of study drug in UX001-CL302.	
Subject analysis set title	Ace-ER 6 g/Day (Parent Study Treatment: Ace-ER 6 g/Day)
Subject analysis set type	Full analysis
Subject analysis set description:	
4 tablets (500 mg Ace-ER each for 2 g per dose) orally 3 times per day in subjects who took Ace-ER in study UX001-CL301	
Subject analysis set title	Ace-ER 6 g/Day (Parent Study Treatment: Placebo)
Subject analysis set type	Full analysis
Subject analysis set description:	
4 tablets (500 mg Ace-ER each for 2 g per dose) orally 3 times per day in subjects who took placebo in study UX001-CL301	

Primary: Number of Subjects With Treatment Emergent Adverse Events (TEAEs), Serious AEs (SAEs), and Discontinuations Due to AEs

End point title	Number of Subjects With Treatment Emergent Adverse Events (TEAEs), Serious AEs (SAEs), and Discontinuations Due to AEs[1]
End point description:	
An AE was defined as any untoward medical occurrence associated with the use of a drug, whether or not considered drug related. An SAE or serious suspected adverse reaction is an AE or suspected adverse reaction that at any dose, in the view of either the Investigator or Ultragenyx, results in any of the following outcomes: death; a life-threatening AE; inpatient hospitalization or prolongation of existing hospitalization; persistent or significant incapacity or disability (substantial disruption of the ability to conduct normal life functions); congenital anomaly/birth defect. TEAEs were defined as any AE that occurred after the first dose of study drug. The severity of all AEs were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03: grade1=mild, grade 2=moderate, grade 3=severe, grade 4=life-threatening, grade 5=death.	
End point type	Primary
End point timeframe:	
From first dose of study drug through the end of treatment plus 30 days (+5 days). Mean (SD) duration of treatment was ---?	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics are presented per protocol.

End point values	Safety Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	142			
Units: subjects				
TEAEs	104			
Serious TEAEs (SAEs)	7			
Deaths	0			
Grade 3 or 4 TEAEs	11			
TEAEs Leading to Study Drug Discontinuation	2			
TEAEs Leading to Study Discontinuation	1			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in HHD UEC Score Over Time

End point title	Change From Baseline in HHD UEC Score Over Time

End point description:

Hand held dynamometry testing was used to measure strength. The maximum voluntary isometric contraction against a dynamometer was used to measure bilateral strength in the following muscle groups: shoulder abductors, wrist extensors and knee extensors. Specialized dynamometers for the measurement of grip and key pinch strength were also used. The total force (in kgf) for each was recorded. The UEC is derived from the sum of the average of the right and left total force (measured in kgf). Analyzed using a repeated measure generalized estimation equation (GEE) model, which includes the baseline value as a covariate.

End point type	Primary

End point timeframe:

Baseline, Weeks 8, 16, 24, 48

End point values	Ace-ER 6 g/Day (Parent Study Treatment: Ace-ER 6 g/Day)	Ace-ER 6 g/Day (Parent Study Treatment: Placebo)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44	43		
Units: kgf				
least squares mean (confidence interval 95%)				
Week 8	0.88 (-0.75 to 2.51)	0.09 (-1.05 to 1.23)		
Week 16	0.10 (-1.47 to 1.67)	-0.26 (-1.26 to 0.74)		
Week 24	-1.40 (-2.92 to 0.12)	-0.49 (-2.13 to 1.15)		
Week 48	-2.24 (-4.95 to 0.47)	-2.18 (-4.30 to -0.07)		

Statistical analyses

Statistical analysis title	Week 8
Comparison groups	Ace-ER 6 g/Day (Parent Study Treatment: Ace-ER 6 g/Day) v Ace-ER 6 g/Day (Parent Study Treatment: Placebo)
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4287 [2]
Method	GEE model
Parameter estimate	LS Mean Difference
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.17
upper limit	2.77

Notes:

[2] - Baseline is fit into the model as a covariate.

Statistical analysis title	Week 16
Comparison groups	Ace-ER 6 g/Day (Parent Study Treatment: Ace-ER 6 g/Day) v Ace-ER 6 g/Day (Parent Study Treatment: Placebo)
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7031 [3]
Method	GEE model
Parameter estimate	LS Mean Difference
Point estimate	0.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.49
upper limit	2.21

Notes:

[3] - Baseline is fit into the model as a covariate.

Statistical analysis title	Week 24
Comparison groups	Ace-ER 6 g/Day (Parent Study Treatment: Ace-ER 6 g/Day) v Ace-ER 6 g/Day (Parent Study Treatment: Placebo)

Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4253 [4]
Method	GEE model
Parameter estimate	LS Mean Difference
Point estimate	-0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.14
upper limit	1.32

Notes:

[4] - Baseline is fit into the model as a covariate.

Statistical analysis title	Week 48
Comparison groups	Ace-ER 6 g/Day (Parent Study Treatment: Ace-ER 6 g/Day) v Ace-ER 6 g/Day (Parent Study Treatment: Placebo)
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9747 [5]
Method	GEE model
Parameter estimate	LS Mean Difference
Point estimate	-0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.49
upper limit	3.38

Notes:

[5] - Baseline is fit into the model as a covariate.

Secondary: Change From Baseline in the GNEM-FAS Expanded Version Mobility Domain Score Over Time

End point title	Change From Baseline in the GNEM-FAS Expanded Version Mobility Domain Score Over Time

End point description:

GNEM-FAS Expanded Version Mobility subscale score has 13 items and ranges from 0 to 52 with higher scores representing greater mobility. Analyzed using a repeated measure GEE model, which includes the baseline value as a covariate.

End point type	Secondary

End point timeframe:

Baseline, Weeks 8, 16, 24, 48

End point values	Ace-ER 6 g/Day (Parent Study Treatment: Ace-ER 6 g/Day)	Ace-ER 6 g/Day (Parent Study Treatment: Placebo)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44	43		
Units: score on a scale				
least squares mean (confidence interval 95%)				
Week 8	-0.12 (-0.66 to 0.42)	0.15 (-0.35 to 0.65)		
Week 16	-0.30 (-0.87 to 0.27)	-0.12 (-0.72 to 0.49)		
Week 24	-0.78 (-1.31 to -0.25)	-0.34 (-0.92 to 0.23)		
Week 48	-0.73 (-1.43 to -0.03)	-0.45 (-1.67 to 0.77)		

Statistical analyses

Statistical analysis title	Week 8
Comparison groups	Ace-ER 6 g/Day (Parent Study Treatment: Placebo) v Ace-ER 6 g/Day (Parent Study Treatment: Ace-ER 6 g/Day)
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4721 [6]
Method	GEE model
Parameter estimate	LS Mean Difference
Point estimate	-0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.01
upper limit	0.47

Notes:

[6] - Baseline is fit into the model as a covariate.

Statistical analysis title	Week 16
Comparison groups	Ace-ER 6 g/Day (Parent Study Treatment: Ace-ER 6 g/Day) v Ace-ER 6 g/Day (Parent Study Treatment: Placebo)
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6611 [7]
Method	GEE model
Parameter estimate	LS Mean Difference
Point estimate	-0.19

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.01
upper limit	0.47

Notes:

[7] - Baseline is fit into the model as a covariate.

Statistical analysis title	Week 24
Comparison groups	Ace-ER 6 g/Day (Parent Study Treatment: Ace-ER 6 g/Day) v Ace-ER 6 g/Day (Parent Study Treatment: Placebo)
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.276 [8]
Method	GEE model
Parameter estimate	LS Mean Difference
Point estimate	-0.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.22
upper limit	0.35

Notes:

[8] - Baseline is fit into the model as a covariate.

Statistical analysis title	Week 48
Comparison groups	Ace-ER 6 g/Day (Parent Study Treatment: Ace-ER 6 g/Day) v Ace-ER 6 g/Day (Parent Study Treatment: Placebo)
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6977 [9]
Method	GEE model
Parameter estimate	LS Mean Difference
Point estimate	-0.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.69
upper limit	1.13

Notes:

[9] - Baseline is fit into the model as a covariate.

Secondary: Change From Baseline on the GNEM-FAS Upper Extremity Domain Score Over Time

End point title	Change From Baseline on the GNEM-FAS Upper Extremity Domain Score Over Time

End point description:

GNEM-FAS Expanded Version Upper Extremity subscale score has 9 items and ranges from 0 to 36 with higher scores representing more skilled, independent use of the arms during functional activity

performance. Analyzed using a repeated measure GEE model, which includes the baseline value as a covariate.

End point type	Secondary

End point timeframe:

Baseline, Weeks 8, 16, 24, 48

End point values	Ace-ER 6 g/Day (Parent Study Treatment: Ace-ER 6 g/Day)	Ace-ER 6 g/Day (Parent Study Treatment: Placebo)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44	43		
Units: score on a scale				
least squares mean (confidence interval 95%)				
Week 8	0.68 (0.15 to 1.22)	-0.02 (-0.55 to 0.51)		
Week 16	0.34 (-0.21 to 0.89)	-0.40 (-0.99 to 0.19)		
Week 24	0.26 (-0.41 to 0.93)	-0.17 (-1.01 to 0.67)		
Week 48	-0.82 (-2.16 to 0.51)	-0.48 (-1.03 to 0.07)		

Statistical analyses

Statistical analysis title	Week 8
Comparison groups	Ace-ER 6 g/Day (Parent Study Treatment: Placebo) v Ace-ER 6 g/Day (Parent Study Treatment: Ace-ER 6 g/Day)
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0648 [10]
Method	GEE model
Parameter estimate	LS Mean Difference
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.04
upper limit	1.45

Notes:

[10] - Baseline is fit into the model as a covariate.

Statistical analysis title	Week 16
Comparison groups	Ace-ER 6 g/Day (Parent Study Treatment: Ace-ER 6 g/Day) v Ace-ER 6 g/Day (Parent Study Treatment: Placebo)

Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0692 [11]
Method	GEE model
Parameter estimate	LS Mean Difference
Point estimate	0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.06
upper limit	1.55

Notes:

[11] - Baseline is fit into the model as a covariate.

Statistical analysis title	Week 24
Comparison groups	Ace-ER 6 g/Day (Parent Study Treatment: Ace-ER 6 g/Day) v Ace-ER 6 g/Day (Parent Study Treatment: Placebo)
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4317 [12]
Method	GEE model
Parameter estimate	LS Mean Difference
Point estimate	0.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.65
upper limit	1.52

Notes:

[12] - Baseline is fit into the model as a covariate.

Statistical analysis title	Week 48
Comparison groups	Ace-ER 6 g/Day (Parent Study Treatment: Ace-ER 6 g/Day) v Ace-ER 6 g/Day (Parent Study Treatment: Placebo)
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6416 [13]
Method	GEE model
Parameter estimate	LS Mean Difference
Point estimate	-0.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.78
upper limit	1.1

Notes:

[13] - Baseline is fit into the model as a covariate.

Secondary: Change From Baseline in HHD Lower Extremity Composite (LEC) Score Over Time

End point title	Change From Baseline in HHD Lower Extremity Composite (LEC) Score Over Time

End point description:

Hand held dynamometry testing was used to measure strength. The maximum voluntary isometric contraction against a dynamometer was used to measure bilateral strength in the following muscle groups: shoulder abductors, wrist extensors and knee extensors. Specialized dynamometers for the measurement of grip and key pinch strength were also used. The total force (in kgf) for each was recorded. The LEC is derived from the sum of the average of the right and left total force (measured in kgf). Analyzed using a repeated measure GEE model, which includes the baseline value as a covariate.

End point type	Secondary

End point timeframe:

Baseline, Weeks 8, 16, 24, and 48

End point values	Ace-ER 6 g/Day (Parent Study Treatment: Ace-ER 6 g/Day)	Ace-ER 6 g/Day (Parent Study Treatment: Placebo)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44	43		
Units: kgf				
arithmetic mean (confidence interval 95%)				
Week 8	0.01 (-2.01 to 2.04)	-0.77 (-3.65 to 2.11)		
Week 16	-1.63 (-3.95 to 0.34)	-0.98 (-3.77 to 1.81)		
Week 24	-0.60 (-3.90 to 2.71)	-0.10 (-3.82 to 3.62)		
Week 48	-0.32 (-4.02 to 3.39)	-4.47 (-7.45 to -1.49)		

Statistical analyses

Statistical analysis title	Week 8
Comparison groups	Ace-ER 6 g/Day (Parent Study Treatment: Ace-ER 6 g/Day) v Ace-ER 6 g/Day (Parent Study Treatment: Placebo)
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6546 [14]
Method	GEE model
Parameter estimate	LS Mean Difference
Point estimate	0.78

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.65
upper limit	4.22

Notes:

[14] - Baseline is fit into the model as a covariate.

Statistical analysis title	Week 16
Comparison groups	Ace-ER 6 g/Day (Parent Study Treatment: Ace-ER 6 g/Day) v Ace-ER 6 g/Day (Parent Study Treatment: Placebo)
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7054 [15]
Method	GEE model
Parameter estimate	LS Mean Difference
Point estimate	-0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.97
upper limit	2.69

Notes:

[15] - Baseline is fit into the model as a covariate.

Statistical analysis title	Week 24
Comparison groups	Ace-ER 6 g/Day (Parent Study Treatment: Ace-ER 6 g/Day) v Ace-ER 6 g/Day (Parent Study Treatment: Placebo)
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8441 [16]
Method	GEE model
Parameter estimate	LS Mean Difference
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.45
upper limit	4.45

Notes:

[16] - Baseline is fit into the model as a covariate.

Statistical analysis title	Week 48
Comparison groups	Ace-ER 6 g/Day (Parent Study Treatment: Ace-ER 6 g/Day) v Ace-ER 6 g/Day (Parent Study Treatment: Placebo)

Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0864 [17]
Method	GEE model
Parameter estimate	LS Mean Difference
Point estimate	4.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.59
upper limit	8.9

Notes:

[17] - Baseline is fit into the model as a covariate.

Secondary: Change From Baseline in the Number of Stands in the Sit-to-Stand Test Over Time

End point title	Change From Baseline in the Number of Stands in the Sit-to-Stand Test Over Time

End point description:

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. Analyzed using a repeated measure GEE model, which includes the baseline value as a covariate.

End point type	Secondary

End point timeframe:

Baseline, Weeks 8, 16, 24, and 48

End point values	Ace-ER 6 g/Day (Parent Study Treatment: Ace-ER 6 g/Day)	Ace-ER 6 g/Day (Parent Study Treatment: Placebo)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44	43		
Units: stands				
least squares mean (confidence interval 95%)				
Week 8	0.02 (-0.43 to 0.46)	-0.05 (-0.61 to 0.51)		
Week 16	-0.04 (-0.49 to 0.40)	0.14 (-0.39 to 0.66)		
Week 24	0.06 (-0.43 to 0.56)	-0.41 (-0.94 to 0.12)		
Week 48	-0.39 (-1.36 to 0.57)	-0.36 (-1.11 to 0.39)		

Statistical analyses

Statistical analysis title	Week 8
Comparison groups	Ace-ER 6 g/Day (Parent Study Treatment: Placebo) v Ace-ER 6 g/Day (Parent Study Treatment: Ace-ER 6 g/Day)
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8603 [18]
Method	GEE model
Parameter estimate	LS Mean Difference
Point estimate	0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.65
upper limit	0.78

Notes:

[18] - Baseline is fit into the model as a covariate.

Statistical analysis title	Week 16
Comparison groups	Ace-ER 6 g/Day (Parent Study Treatment: Ace-ER 6 g/Day) v Ace-ER 6 g/Day (Parent Study Treatment: Placebo)
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6154 [19]
Method	GEE model
Parameter estimate	LS Mean Difference
Point estimate	-0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.86
upper limit	0.51

Notes:

[19] - Baseline is fit into the model as a covariate.

Statistical analysis title	Week 24
Comparison groups	Ace-ER 6 g/Day (Parent Study Treatment: Ace-ER 6 g/Day) v Ace-ER 6 g/Day (Parent Study Treatment: Placebo)
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1999 [20]
Method	GEE model
Parameter estimate	LS Mean Difference
Point estimate	0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.25
upper limit	1.2

Notes:

[20] - Baseline is fit into the model as a covariate.

Statistical analysis title	Week 48
Comparison groups	Ace-ER 6 g/Day (Parent Study Treatment: Ace-ER 6 g/Day) v Ace-ER 6 g/Day (Parent Study Treatment: Placebo)
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9568 [21]
Method	GEE model
Parameter estimate	LS Mean Difference
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.25
upper limit	1.18

Notes:

[21] - Baseline is fit into the model as a covariate.

Secondary: Change From Baseline in Number of Lifts in the 30-Second Weighted Arm Lift Test Over Time

End point title	Change From Baseline in Number of Lifts in the 30-Second Weighted Arm Lift Test Over Time

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. Analyzed using a repeated measure GEE model, which includes the baseline value as a covariate.

End point type	Secondary

End point timeframe:

Baseline, Weeks 8, 16, 24, and 48

End point values	Ace-ER 6 g/Day (Parent Study Treatment: Ace-ER 6 g/Day)	Ace-ER 6 g/Day (Parent Study Treatment: Placebo)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44	43		
Units: lifts				
least squares mean (confidence interval 95%)				
Week 8	0.26 (-1.00 to 1.52)	-0.19 (-0.90 to 0.53)		
Week 16	0.03 (-1.22 to 1.27)	0.59 (-0.50 to 1.68)		
Week 24	0.13 (-0.98 to 1.24)	-0.14 (-1.33 to 1.06)		
Week 48	-1.58 (-3.60 to 0.45)	-1.17 (-2.55 to 0.22)		

Statistical analyses

Statistical analysis title	Week 8
Comparison groups	Ace-ER 6 g/Day (Parent Study Treatment: Ace-ER 6 g/Day) v Ace-ER 6 g/Day (Parent Study Treatment: Placebo)
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5447 [22]
Method	GEE model
Parameter estimate	LS Mean Difference
Point estimate	0.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	1.9

Notes:

[22] - Baseline is fit into the model as a covariate.

Statistical analysis title	Week 16
Comparison groups	Ace-ER 6 g/Day (Parent Study Treatment: Ace-ER 6 g/Day) v Ace-ER 6 g/Day (Parent Study Treatment: Placebo)
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5051 [23]
Method	GEE model
Parameter estimate	LS Mean Difference
Point estimate	-0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.22
upper limit	1.09

Notes:

[23] - Baseline is fit into the model as a covariate.

Statistical analysis title	Week 24
Comparison groups	Ace-ER 6 g/Day (Parent Study Treatment: Ace-ER 6 g/Day) v Ace-ER 6 g/Day (Parent Study Treatment: Placebo)

Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7478 [24]
Method	GEE model
Parameter estimate	LS Mean Difference
Point estimate	0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.36
upper limit	1.9

Notes:

[24] - Baseline is fit into the model as a covariate.

Statistical analysis title	Week 48
Comparison groups	Ace-ER 6 g/Day (Parent Study Treatment: Ace-ER 6 g/Day) v Ace-ER 6 g/Day (Parent Study Treatment: Placebo)
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7429 [25]
Method	GEE model
Parameter estimate	LS Mean Difference
Point estimate	-0.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.86
upper limit	2.04

Notes:

[25] - Baseline is fit into the model as a covariate.

Secondary: Change From Baseline in Meters Walked in 6MWT Over Time

End point title	Change From Baseline in Meters Walked in 6MWT Over Time

End point description:

The total distance walked (meters) in a 6-minute period was measured. Analyzed using a repeated measure GEE model, which includes the baseline value as a covariate.

End point type	Secondary

End point timeframe:

Baseline, Weeks 8, 16, 24, and 48

End point values	Ace-ER 6 g/Day (Parent Study Treatment: Ace-ER 6 g/Day)	Ace-ER 6 g/Day (Parent Study Treatment: Placebo)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44	43		
Units: meters				
least squares mean (confidence interval 95%)				
Week 8	-1.40 (-8.34 to 5.53)	-3.41 (-7.92 to 1.10)		
Week 16	-3.91 (-12.03 to 4.20)	-1.93 (-8.32 to 4.47)		
Week 24	-2.73 (-10.81 to 5.35)	-6.88 (-13.43 to -0.33)		
Week 48	-13.91 (-25.58 to -2.25)	-21.89 (-38.51 to -5.28)		

Statistical analyses

Statistical analysis title	Week 8
Comparison groups	Ace-ER 6 g/Day (Parent Study Treatment: Ace-ER 6 g/Day) v Ace-ER 6 g/Day (Parent Study Treatment: Placebo)
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6434 [26]
Method	GEE model
Parameter estimate	LS Mean Difference
Point estimate	2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.48
upper limit	10.49

Notes:

[26] - Baseline is fit into the model as a covariate.

Statistical analysis title	Week 16
Comparison groups	Ace-ER 6 g/Day (Parent Study Treatment: Ace-ER 6 g/Day) v Ace-ER 6 g/Day (Parent Study Treatment: Placebo)
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7118 [27]
Method	GEE model
Parameter estimate	LS Mean Difference
Point estimate	-1.99

Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.53
upper limit	8.55

Notes:

[27] - Baseline is fit into the model as a covariate.

Statistical analysis title	Week 24
Comparison groups	Ace-ER 6 g/Day (Parent Study Treatment: Ace-ER 6 g/Day) v Ace-ER 6 g/Day (Parent Study Treatment: Placebo)
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4399 [28]
Method	GEE model
Parameter estimate	LS Mean Difference
Point estimate	4.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.39
upper limit	14.69

Notes:

[28] - Baseline is fit into the model as a covariate.

Statistical analysis title	Week 48
Comparison groups	Ace-ER 6 g/Day (Parent Study Treatment: Ace-ER 6 g/Day) v Ace-ER 6 g/Day (Parent Study Treatment: Placebo)
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.443 [29]
Method	GEE model
Parameter estimate	LS Mean Difference
Point estimate	7.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.41
upper limit	28.37

Notes:

[29] - Baseline is fit into the model as a covariate.

Secondary: Change From Baseline in Percent Predicted Meters Walked in 6MWT Over Time

End point title	Change From Baseline in Percent Predicted Meters Walked in 6MWT Over Time

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. Predicted 6MWT 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. Analyzed using a repeated measure GEE model, which includes the baseline value as a covariate.

End point type	Secondary
End point timeframe:	
Baseline, Weeks 8, 16, 24, and 48	

End point values	Ace-ER 6 g/Day (Parent Study Treatment: Ace-ER 6 g/Day)	Ace-ER 6 g/Day (Parent Study Treatment: Placebo)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44	43		
Units: percent of predicted distance				
least squares mean (confidence interval 95%)				
Week 8	-0.17 (-1.12 to 0.79)	-0.45 (-1.09 to 0.20)		
Week 16	-0.49 (-1.60 to 0.61)	-0.24 (-1.15 to 0.67)		
Week 24	-0.38 (-1.49 to 0.73)	-0.96 (-1.88 to -0.03)		
Week 48	-1.94 (-3.56 to -0.31)	-2.93 (-5.04 to -0.81)		

Statistical analyses

Statistical analysis title	Week 8
Comparison groups	Ace-ER 6 g/Day (Parent Study Treatment: Ace-ER 6 g/Day) v Ace-ER 6 g/Day (Parent Study Treatment: Placebo)
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6428 [30]
Method	GEE model
Parameter estimate	LS Mean Difference
Point estimate	0.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	1.46

Notes:

[30] - Baseline is fit into the model as a covariate.

Statistical analysis title	Week 16
Comparison groups	Ace-ER 6 g/Day (Parent Study Treatment: Ace-ER 6 g/Day) v Ace-ER 6 g/Day (Parent Study Treatment: Placebo)

Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7334 [31]
Method	GEE model
Parameter estimate	LS Mean Difference
Point estimate	-0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.72
upper limit	1.21

Notes:

[31] - Baseline is fit into the model as a covariate.

Statistical analysis title	Week 24
Comparison groups	Ace-ER 6 g/Day (Parent Study Treatment: Ace-ER 6 g/Day) v Ace-ER 6 g/Day (Parent Study Treatment: Placebo)
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4409 [32]
Method	GEE model
Parameter estimate	LS Mean Difference
Point estimate	0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.89
upper limit	2.04

Notes:

[32] - Baseline is fit into the model as a covariate.

Statistical analysis title	Week 48
Comparison groups	Ace-ER 6 g/Day (Parent Study Treatment: Ace-ER 6 g/Day) v Ace-ER 6 g/Day (Parent Study Treatment: Placebo)
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4687 [33]
Method	GEE model
Parameter estimate	LS Mean Difference
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.69
upper limit	3.68

Notes:

[33] - Baseline is fit into the model as a covariate.

Secondary: Change From Baseline in Total Force in Knee Extensors Over Time

End point title	Change From Baseline in Total Force in Knee Extensors Over Time

End point description:

Hand held dynamometry testing was used to measure strength. The maximum voluntary isometric contraction against a dynamometer was used to measure bilateral strength in the following muscle groups: shoulder abductors, wrist extensors and knee extensors. Specialized dynamometers for the measurement of grip and key pinch strength were also used. The total force (in kgf) for each was recorded. Bilateral total force was defined as the average of the right and left force (measured in kgf). Analyzed using a repeated measure GEE model, which includes the baseline value as a covariate.

End point type	Secondary

End point timeframe:

Baseline, Weeks 8, 16, 24, and 48

End point values	Ace-ER 6 g/Day (Parent Study Treatment: Ace-ER 6 g/Day)	Ace-ER 6 g/Day (Parent Study Treatment: Placebo)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44	43		
Units: kgf				
least squares mean (confidence interval 95%)				
Week 8	0.50 (-0.77 to 1.78)	-0.64 (-1.53 to 0.25)		
Week 16	-0.95 (-2.03 to 0.14)	-0.75 (-2.05 to 0.55)		
Week 24	0.33 (-1.33 to 2.00)	-0.46 (-2.15 to 1.23)		
Week 48	0.63 (-2.30 to 3.56)	-0.08 (-2.28 to 2.13)		

Statistical analyses

Statistical analysis title	Week 8
Comparison groups	Ace-ER 6 g/Day (Parent Study Treatment: Ace-ER 6 g/Day) v Ace-ER 6 g/Day (Parent Study Treatment: Placebo)
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.15 [34]
Method	GEE model
Parameter estimate	LS Mean Difference
Point estimate	1.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.41
upper limit	2.69

Notes:

[34] - Baseline is fit into the model as a covariate.

Statistical analysis title	Week 16
Comparison groups	Ace-ER 6 g/Day (Parent Study Treatment: Ace-ER 6 g/Day) v Ace-ER 6 g/Day (Parent Study Treatment: Placebo)
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8188 [35]
Method	GEE model
Parameter estimate	LS Mean Difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.89
upper limit	1.49

Notes:

[35] - Baseline is fit into the model as a covariate.

Statistical analysis title	Week 24
Comparison groups	Ace-ER 6 g/Day (Parent Study Treatment: Ace-ER 6 g/Day) v Ace-ER 6 g/Day (Parent Study Treatment: Placebo)
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5122 [36]
Method	GEE model
Parameter estimate	LS Mean Difference
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.58
upper limit	3.17

Notes:

[36] - Baseline is fit into the model as a covariate.

Statistical analysis title	Week 48
Comparison groups	Ace-ER 6 g/Day (Parent Study Treatment: Ace-ER 6 g/Day) v Ace-ER 6 g/Day (Parent Study Treatment: Placebo)
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7022 [37]
Method	GEE model
Parameter estimate	LS Mean Difference
Point estimate	0.72

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.96
upper limit	4.4

Notes:

[37] - Baseline is fit into the model as a covariate.

Secondary: Change From Baseline in Percent Predicted Total Force in Knee Extensors Over Time

End point title	Change From Baseline in Percent Predicted Total Force in Knee Extensors Over Time

End point description:

The percent predicted total force value of lower extremity muscle strength in the knee extensors was determined based on reference equations adjusting for age, gender, height, and weight. Analyzed using a repeated measure GEE model, which includes the baseline value as a covariate.

End point type	Secondary

End point timeframe:

Baseline, Weeks 8, 16, 24, and 48

End point values	Ace-ER 6 g/Day (Parent Study Treatment: Ace-ER 6 g/Day)	Ace-ER 6 g/Day (Parent Study Treatment: Placebo)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44	43		
Units: percent of predicted total force (kgf)				
least squares mean (confidence interval 95%)				
Week 8	-0.98 (-1.78 to -0.19)	-1.17 (-2.44 to 0.09)		
Week 16	-0.59 (-1.48 to 0.31)	-1.25 (-2.43 to -0.07)		
Week 24	-0.70 (-1.92 to 0.53)	-0.85 (-2.53 to 0.83)		
Week 48	-1.02 (-2.17 to 0.13)	-3.10 (-4.40 to -1.80)		

Statistical analyses

Statistical analysis title	Week 8
Comparison groups	Ace-ER 6 g/Day (Parent Study Treatment: Ace-ER 6 g/Day) v Ace-ER 6 g/Day (Parent Study Treatment: Placebo)

Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7906 [38]
Method	GEE model
Parameter estimate	LS Mean Difference
Point estimate	0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.22
upper limit	1.6

Notes:

[38] - Baseline is fit into the model as a covariate.

Statistical analysis title	Week 16
Comparison groups	Ace-ER 6 g/Day (Parent Study Treatment: Ace-ER 6 g/Day) v Ace-ER 6 g/Day (Parent Study Treatment: Placebo)
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3531 [39]
Method	GEE model
Parameter estimate	LS Mean Difference
Point estimate	0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.74
upper limit	2.07

Notes:

[39] - Baseline is fit into the model as a covariate.

Statistical analysis title	Week 24
Comparison groups	Ace-ER 6 g/Day (Parent Study Treatment: Ace-ER 6 g/Day) v Ace-ER 6 g/Day (Parent Study Treatment: Placebo)
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8846 [40]
Method	GEE model
Parameter estimate	LS Mean Difference
Point estimate	0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.92
upper limit	2.23

Notes:

[40] - Baseline is fit into the model as a covariate.

Statistical analysis title	Week 48
Comparison groups	Ace-ER 6 g/Day (Parent Study Treatment: Ace-ER 6 g/Day) v Ace-ER 6 g/Day (Parent Study Treatment: Placebo)
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0168 [41]
Method	GEE model
Parameter estimate	LS Mean Difference
Point estimate	2.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.38
upper limit	3.79

Notes:

[41] - Baseline is fit into the model as a covariate.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug through the end of treatment plus 30 days (+5 days). Mean (SD) duration of treatment was ---?

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:

4 tablets (500 mg Ace-ER each for 2 g per dose) orally 3 times per day

Serious adverse events	Ace-ER 6 g/day		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 142 (4.93%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Biopsy kidney			
subjects affected / exposed	1 / 142 (0.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant melanoma in situ			
subjects affected / exposed	1 / 142 (0.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 142 (0.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	1 / 142 (0.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 142 (0.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal pain			
subjects affected / exposed	1 / 142 (0.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Atypical pneumonia			
subjects affected / exposed	1 / 142 (0.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Ace-ER 6 g/day		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	83 / 142 (58.45%)		
Investigations			
Haemoglobin decreased			
subjects affected / exposed	1 / 142 (0.70%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	30 / 142 (21.13%)		
occurrences (all)	67		
Laceration			
subjects affected / exposed	5 / 142 (3.52%)		
occurrences (all)	8		
Procedural pain			

subjects affected / exposed	4 / 142 (2.82%)		
occurrences (all)	7		
Skin abrasion			
subjects affected / exposed	7 / 142 (4.93%)		
occurrences (all)	8		
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 142 (3.52%)		
occurrences (all)	6		
Extensor plantar response			
subjects affected / exposed	1 / 142 (0.70%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	8 / 142 (5.63%)		
occurrences (all)	11		
Hypotonia			
subjects affected / exposed	1 / 142 (0.70%)		
occurrences (all)	1		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	8 / 142 (5.63%)		
occurrences (all)	24		
Influenza like illness			
subjects affected / exposed	7 / 142 (4.93%)		
occurrences (all)	10		
Peripheral swelling			
subjects affected / exposed	4 / 142 (2.82%)		
occurrences (all)	5		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	4 / 142 (2.82%)		
occurrences (all)	5		
Diarrhoea			
subjects affected / exposed	10 / 142 (7.04%)		
occurrences (all)	12		
Flatulence			

subjects affected / exposed	9 / 142 (6.34%)		
occurrences (all)	9		
Nausea			
subjects affected / exposed	7 / 142 (4.93%)		
occurrences (all)	7		
Reproductive system and breast disorders			
Vulvovaginal pruritus			
subjects affected / exposed	1 / 142 (0.70%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 142 (4.93%)		
occurrences (all)	8		
Oropharyngeal pain			
subjects affected / exposed	7 / 142 (4.93%)		
occurrences (all)	7		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	17 / 142 (11.97%)		
occurrences (all)	22		
Back pain			
subjects affected / exposed	13 / 142 (9.15%)		
occurrences (all)	16		
Muscular weakness			
subjects affected / exposed	6 / 142 (4.23%)		
occurrences (all)	8		
Musculoskeletal pain			
subjects affected / exposed	11 / 142 (7.75%)		
occurrences (all)	16		
Neck pain			
subjects affected / exposed	5 / 142 (3.52%)		
occurrences (all)	7		
Pain in extremity			
subjects affected / exposed	10 / 142 (7.04%)		
occurrences (all)	13		

Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	8 / 142 (5.63%)		
occurrences (all)	12		
Upper respiratory tract infection			
subjects affected / exposed	3 / 142 (2.11%)		
occurrences (all)	5		
Urinary tract infection			
subjects affected / exposed	5 / 142 (3.52%)		
occurrences (all)	7		
Viral upper respiratory tract infection			
subjects affected / exposed	6 / 142 (4.23%)		
occurrences (all)	7		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 June 2016	1. The protocol was amended to allow for the inclusion of subjects who complete the UX001-CL202 study. This change affected multiple sections of the protocol, including the synopsis, Table 2.1, and Inclusion Criterion 1 (Section 7.3.1). Subjects enrolling from the UX001-CL202 study will follow the same schedule of events as subjects who roll over from the UX001-CL301 study. 2. With regard to Change #1 above, the amendment clarifies that subjects who rollover from UX001-CL202 will receive 6 g/day of Ace-ER. No subjects will receive 12 g/day in this study. 3. Treatment duration language changed to remove "until commercial availability of study drug in subject's region." This change affected multiple sections of the protocol, including Synopsis, Figure 2.1 and Section 7. The treatment duration on the study will be 24 Months. 4. Table 7.5.5.5.1 was updated to include blood/RBC and leukocyte esterase to the urinalysis panel and to add a footnote indicating that microscopic evaluation will be conducted for abnormal urine test results. 5. Language was added to the synopsis and multiple sections of the protocol instructing that for UX001-CL202 subjects, assessments that cannot be safely performed due to disease progression should not be administered. 6. The number of samples drawn from each subject (Table 7.5.5.5.1.1) was increased for the serum sialic acid assessments from 2 samples to 5 samples. The total volume of blood sample to be obtained increased from 87 mL to 108 mL for subjects rolling over from UX001-CL203 and from 108 to 129.5 for subjects rolling over from UX001-CL301. 7. Record Retention: Section 8.4.3 has been updated to state that all study records must be retained for at least 25 years after the end of the clinical trial or in accordance with national law.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

No efficacy result summaries or analyses were performed for subjects rolling over from UX001-CL202 or UX001-CL203 because of the limited data from those subjects due to the early study closure.

Notes: