Clinical trial results:
A Phase 2 Open-label study to Evaluate the Safety of Aceneuramic Acid Extended Release (Ace-ER) Tablets in GNE Myopathy (GNEM) (also known as Hereditary Inclusion Body Myopathy (HIBM)) patients with Severe Ambulatory Impairment

Summary

EudraCT number	2015-004553-41
Trial protocol	BG
Global end of trial date	10 January 2018

Results information

Result version number	v1
This version publication date	23 January 2019
First version publication date	23 January 2019

Trial information

Trial identification

Sponsor protocol code	UX001-CL203

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02731690
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 primary objective of this Phase 2 study is to evaluate the safety of open-label 6 g/day Ace-ER in GNEM participants with
severe ambulatory impairment.

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	29 April 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	Bulgaria: 17
Country: Number of subjects enrolled	United States: 22
Country: Number of subjects enrolled	Canada: 3
Worldwide total number of subjects	42
EEA total number of subjects	17

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)	38
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects were screened up to 28 days before the Baseline Visit.

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	UX001 6g/Day

Arm description:

Open-label UX001 6000 mg (6 g) total daily dose administered orally divided into a 3-times-daily regimen.

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

Dosage and administration details:

6000 mg (6 g) total daily dose administered orally divided into a 3-times-daily regimen.

Number of subjects in period 1	UX001 6g/Day
Started	42
Completed	12
Not completed	30
Consent withdrawn by subject	3
Adverse Event	1
Discontinuation of Study by Sponsor	26

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	42	42	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	46.0		
standard deviation	± 13.97	-	
Gender categorical Units: Subjects			
Female	25	25	
Male	17	17	
Ethnicity Units: Subjects			
Hispanic or Latino	0	0	
Not Hispanic or Latino	42	42	
Unknown or Not Reported	0	0	
Race Units: Subjects			
White	31	31	
Asian	2	2	
Other (Not Specified)	9	9	
Glucosamine (UDP-N-acetyl)-2-epimerase Myopathy Functional Activities Scale(GNEM-FAS) Mobility Score			
GNEM-FAS Expanded Version Mobility subscale scores have 13 items and range from 0 to 52 with higher scores representing greater mobility.			
Units: units on a scale			
arithmetic mean			
standard deviation	±	-	
GNEM-FAS Upper Extremity Domain Score			
GNEM-FAS Expanded Version Upper Extremity subscale scores have 9 items and range from 0 to 36 with higher scores representing more skilled, independent use of the arms during functional activity performance.			
Units: units on a scale			
arithmetic mean			
standard deviation	±	-	
GNEM-FAS Self-Care Domain Score			
GNEM-FAS Expanded Version Self-Care subscale scores have 8 items range from 0 to 32 with higher scores representing greater independence with functional care activities.			
Units: units on a scale			
arithmetic mean			

standard deviation	±	-	
GNEM-FAS Total Score			
GNEM-FAS Expanded Version Total Score were calculated as the sum of the subscale Scores range from 0 to 120 with higher scores representing greater independence with functional activities.			
Units: units on a scale arithmetic mean standard deviation	±	-	
Hand-Held Dynamometry (HHD) Raw Strength: Average Grip			
The highest force value collected using hand held dynamometer for each muscle group was used for data analysis.			
Units: kg arithmetic mean standard deviation	±	-	
HHD Raw Strength: Average Shoulder Abduction			
The highest force value collected using hand held dynamometer for each muscle group was used for data analysis.			
Units: kg arithmetic mean standard deviation	±	-	
HHD Raw Strength: Average Wrist Extension			
The highest force value collected using hand held dynamometer for each muscle group was used for data analysis.			
Units: kg arithmetic mean standard deviation	±	-	
HHD Lower Extremity Muscle Strength: Average Knee Extension			
The highest force value collected using hand held dynamometer for each muscle group was used for data analysis.			
Units: kg arithmetic mean standard deviation	±	-	
HHD Raw Strength: Key Pinch			
The highest force value collected using hand held dynamometer for each muscle group was used for data analysis.			
Units: kg 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 with a baseline measurement and at least 1 postbaseline measurement.	
Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis
Subject analysis set description: all enrolled subjects who received at least 1 dose of study drug.	

Reporting group values	Full Analysis Set	Safety Analysis Set	
Number of subjects	41	42	
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)			
Glucosamine (UDP-N-acetyl)-2-epimerase Myopathy Functional Activities Scale(GNEM-FAS) Mobility Score			
GNEM-FAS Expanded Version Mobility subscale scores have 13 items and range from 0 to 52 with higher scores representing greater mobility.			
Units: units on a scale arithmetic mean standard deviation	 10.63 ± 7.816	 ±	
GNEM-FAS Upper Extremity Domain Score			
GNEM-FAS Expanded Version Upper Extremity subscale scores have 9 items and range from 0 to 36 with higher scores representing more skilled, independent use of the arms during functional activity performance.			
Units: units on a scale arithmetic mean standard deviation	 15.20 ± 8.897	 ±	
GNEM-FAS Self-Care Domain Score			
GNEM-FAS Expanded Version Self-Care subscale scores have 8 items range from 0 to 32 with higher scores representing greater independence with functional care activities.			
Units: units on a scale arithmetic mean standard deviation	 13.00 ± 7.413	 ±	
GNEM-FAS Total Score			
GNEM-FAS Expanded Version Total Score were calculated as the sum of the subscale Scores range from 0 to 120 with higher scores representing greater independence with functional activities.			
Units: units on a scale arithmetic mean standard deviation	 38.83 ± 23.116	 ±	
Hand-Held Dynamometry (HHD) Raw Strength: Average Grip			

The highest force value collected using hand held dynamometer for each muscle group was used for data analysis.			
Units: kg			
arithmetic mean	5.535		
standard deviation	± 7.6778	±	
HHD Raw Strength: Average Shoulder Abduction			
The highest force value collected using hand held dynamometer for each muscle group was used for data analysis.			
Units: kg			
arithmetic mean	3.880		
standard deviation	± 4.4583	±	
HHD Raw Strength: Average Wrist Extension			
The highest force value collected using hand held dynamometer for each muscle group was used for data analysis.			
Units: kg			
arithmetic mean	3.532		
standard deviation	± 3.5177	±	
HHD Lower Extremity Muscle Strength: Average Knee Extension			
The highest force value collected using hand held dynamometer for each muscle group was used for data analysis.			
Units: kg			
arithmetic mean	10.50		
standard deviation	± 8.001	±	
HHD Raw Strength: Key Pinch			
The highest force value collected using hand held dynamometer for each muscle group was used for data analysis.			
Units: kg			
arithmetic mean	1.790		
standard deviation	± 2.1614	±	

End points

End points reporting groups

Reporting group title	UX001 6g/Day
Reporting group description:	
Open-label UX001 6000 mg (6 g) total daily dose administered orally divided into a 3-times-daily regimen.	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
all subjects with a baseline measurement and at least 1 postbaseline measurement.	
Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
all enrolled subjects who received at least 1 dose of study drug.	

Primary: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs), Serious TEAEs, and TEAEs Leading to Discontinuation

End point title	Number of Subjects With Treatment-Emergent Adverse Events (TEAEs), Serious TEAEs, and TEAEs Leading to Discontinuation[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.	
End point type	Primary
End point timeframe:	
48 Weeks (plus 30 [+5] days for participants not enrolling in extension study)	

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	42			
Units: subjects				
TEAEs	30			
Treatment-Related TEAEs	18			
Treatment-Related Serious TEAEs	0			
Serious TEAEs	1			
TEAEs Causing Study Drug Discontinuation	1			
TEAEs Causing Study Discontinuation	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Taking Prior and Concomitant Medications

End point title	Number of Subjects Taking Prior and Concomitant Medications

End point description:

Prior medications are any medications which started before the date of the first dose of investigational product. Concomitant medications are any medications that are taken on or after the date of the first dose of investigational product excluding concomitant medications started after the date of the last dose of investigational product.

End point type	Secondary

End point timeframe:

48 weeks

End point values	Safety Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	42			
Units: subjects				
Prior Medications	31			
Concomitant Medications	33			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Clinically Significant Changes From Baseline In Physical Examinations

End point title	Number of Subjects With Clinically Significant Changes From Baseline In Physical Examinations

End point description:

Complete physical examinations included assessments of general appearance; head, eyes, ears, nose, and throat; the cardiovascular, dermatologic, lymphatic, respiratory, GI, musculoskeletal, and neurologic systems. The neurologic system examination included assessments of cognition, cranial nerves, motor function, coordination and gait, reflexes, and sensory function. Brief physical examinations included assessments of general appearance, cardiovascular and respiratory systems, and a focus on any presenting complaints.

End point type	Secondary

End point timeframe:

48 weeks

End point values	Safety Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	42			
Units: subjects	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Clinically Significant Changes From Baseline In Vital Signs

End point title	Number of Subjects With Clinically Significant Changes From Baseline In Vital Signs

End point description:

Vital signs included seated systolic blood pressure and diastolic blood pressure, heart rate, respiration rate, and temperature.

End point type	Secondary

End point timeframe:

48 weeks

End point values	Safety Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	42			
Units: subjects	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Clinically Significant Changes From Baseline In Clinical Laboratory Results

End point title	Number of Subjects With Clinically Significant Changes From Baseline In Clinical Laboratory Results

End point description:

The clinical laboratory evaluations performed included serum chemistry, complete blood count (hematology), and urinalysis.

End point type	Secondary

End point timeframe:

48 weeks

End point values	Safety Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	42			
Units: subjects				
Hematology	0			
Clinical Chemistry	2			
Urinalysis	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Overall Suicidal Behaviors and/or Ideation at Baseline and Post-Baseline

End point title	Number of Participants With Overall Suicidal Behaviors and/or Ideation at Baseline and Post-Baseline

End point description:

As evaluated by the Columbia Suicide Severity Rating Scale (C-SSRS), a participant-rated questionnaire to assess suicidal ideation, suicidal behavior, actual attempts (yes or no responses).

End point type	Secondary

End point timeframe:

48 weeks

End point values	Safety Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	42			
Units: subjects				
Overall Suicidal Behaviors: Baseline	1			
Overall Suicidal Behaviors: Post-Baseline	0			
Non-Suicide Self-Injurious Behavior: Baseline	0			
Non-Suicide Self-Injurious Behavior: Post-Baseline	0			
Completed Suicide: Post-Baseline	0			
Overall Suicidal Ideation: Baseline	7			
Overall Suicidal Ideation: Post-Baseline	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in GNEM-FAS Expanded Version Mobility Domain Subscale Scores Over Time

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

End point description:

GNEM-FAS Expanded Version Mobility subscale scores have 13 items and range from 0 to 52 with higher scores representing greater mobility. Analyzed using a repeated measure generalized estimation equation (GEE) model, which includes the change from baseline as the dependent variable, visit as a fixed factor, and the baseline value as a covariate. Compound symmetry is used as the covariance structure.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12, 24, 36, and 48

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	41[2]			
Units: units on a scale				
least squares mean (confidence interval 95%)				
Week 12	0.16 (-0.33 to 0.64)			
Week 24	-0.65 (-1.56 to 0.27)			
Week 36	-0.69 (-1.57 to 0.18)			
Week 48	-1.03 (-2.15 to 0.09)			

Notes:

[2] - P-values: Week 12=0.5303; Week 24=0.1646; Week 36=0.1189; Week 48=0.0706

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in GNEM-FAS Expanded Version Upper Extremity Domain Subscale Scores Over Time

End point title	Change From Baseline in GNEM-FAS Expanded Version Upper Extremity Domain Subscale Scores Over Time

End point description:

GNEM-FAS Expanded Version Upper Extremity subscale scores have 9 items and range 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 change from baseline as the dependent variable, visit as a fixed factor, and the baseline value as a covariate. Compound symmetry is used as the covariance structure.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12, 24, 36, and 48

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	41[3]			
Units: units on a scale				
least squares mean (confidence interval 95%)				
Week 12	0.57 (-0.05 to 1.19)			
Week 24	-0.62 (-1.50 to 0.26)			
Week 36	-0.51 (-1.58 to 0.55)			
Week 48	-1.91 (-3.93 to 0.11)			

Notes:

[3] - P-values: Week 12=0.0715; Week 24=0.1697; Week 36=0.3428; Week 48=0.0642

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in GNEM-FAS Expanded Version Self-Care Domain Subscale Scores Over Time

End point title	Change From Baseline in GNEM-FAS Expanded Version Self-Care Domain Subscale Scores Over Time

End point description:

GNEM-FAS Expanded Version Self-Care subscale scores have 8 items range from 0 to 32 with higher scores representing greater independence with functional care activities. Analyzed using a repeated measure GEE model, which includes the change from baseline as the dependent variable, visit as a fixed factor, and the baseline value as a covariate. Compound symmetry is used as the covariance structure.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12, 24, 36, and 48

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	41[4]			
Units: units on a scale				
least squares mean (confidence interval 95%)				
Week 12	-0.39 (-0.79 to 0.01)			
Week 24	-0.71 (-1.43 to 0.01)			
Week 36	-0.83 (-1.64 to -0.02)			
Week 48	-0.40 (-1.78 to 0.98)			

Notes:

[4] - P-values: Week 12=0.0568; Week 24=0.0533; Week 36=0.0459; Week 48=0.5678

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in GNEM-FAS Expanded Version Total Scores Over Time

End point title	Change From Baseline in GNEM-FAS Expanded Version Total Scores Over Time

End point description:

GNEM-FAS Expanded Version Total Score were calculated as the sum of the subscale Scores range from 0 to 120 with higher scores representing greater independence with functional activities. Analyzed using a repeated measure GEE model, which includes the change from baseline as the dependent variable, visit as a fixed factor, and the baseline value as a covariate. Compound symmetry is used as the covariance structure.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12, 24, 36, and 48

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	41[5]			
Units: units on a scale				
least squares mean (confidence interval 95%)				
Week 12	0.35 (-0.89 to 1.58)			
Week 24	-1.95 (-3.87 to -0.03)			
Week 36	-2.02 (-4.46 to 0.42)			
Week 48	-3.34 (-6.90 to 0.22)			

Notes:

[5] - P-values: Week 12=0.5810; Week 24=0.0465; Week 36=0.1047; Week 48=0.0661

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in HHD Raw Strength (Grip) Over Time

End point title	Change From Baseline in HHD Raw Strength (Grip) Over Time

End point description:

The highest force value collected using hand held dynamometer for each muscle group was used for data analysis. Analyzed using a repeated measure GEE model, which includes the change from baseline as the dependent variable, visit as a fixed factor, and the baseline value as a covariate. Compound symmetry is used as the covariance structure.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12, 24, 36, and 48

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	41[6]			
Units: kg				
least squares mean (confidence interval 95%)				
Week 12	0.258 (-0.103 to 0.620)			
Week 24	0.128 (-0.377 to 0.632)			
Week 36	0.038 (-0.724 to 0.799)			
Week48	-0.261 (-1.325 to 0.803)			

Notes:

[6] - P-values: Week 12=0.1615; Week 24=0.6201; Week 36=0.9229; Week 48=0.6307

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in HHD Raw Strength (Shoulder Abductors) Over Time

End point title	Change From Baseline in HHD Raw Strength (Shoulder Abductors) Over Time

End point description:

The highest force value collected using hand held dynamometer for each muscle group was used for data analysis. Analyzed using a repeated measure GEE model, which includes the change from baseline as the dependent variable, visit as a fixed factor, and the baseline value as a covariate. Compound symmetry is used as the covariance structure.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12, 24, 36, and 48

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	41[7]			
Units: kg				
least squares mean (confidence interval 95%)				
Week 12	0.339 (0.085 to 0.592)			
Week 24	0.379 (-0.228 to 0.987)			
Week 36	0.437 (0.075 to 0.800)			
Week 48	-0.277 (-0.698 to 0.144)			

Notes:

[7] - P-values: Week 12=0.0088; Week 24=0.2213; Week 36=0.0180; Week 48=0.1970

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in HHD Raw Strength (Wrist Extensors) Over Time

End point title	Change From Baseline in HHD Raw Strength (Wrist Extensors) Over Time

End point description:

The highest force value collected using hand held dynamometer for each muscle group was used for data analysis. Analyzed using a repeated measure GEE model, which includes the change from baseline as the dependent variable, visit as a fixed factor, and the baseline value as a covariate. Compound symmetry is used as the covariance structure.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12, 24, 36, and 48

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	41[8]			
Units: kg				
least squares mean (confidence interval 95%)				
Week 12	0.235 (-0.024 to 0.495)			
Week 24	0.152 (-0.486 to 0.791)			
Week 36	0.358 (-0.228 to 0.943)			
Week 48	-0.123 (-0.924 to 0.678)			

Notes:

[8] - P-values: Week 12=0.0752; Week 24=0.6403; Week 36=0.2316; Week 48=0.7635

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in HHD Muscle Strength in Knee Extensors Over Time

End point title	Change From Baseline in HHD Muscle Strength in Knee Extensors Over Time

End point description:

The highest force value collected using hand held dynamometer for each muscle group was used for data analysis. Analyzed using a repeated measure GEE model, which includes the change from baseline

as the dependent variable, visit as a fixed factor, and the baseline value as a covariate. Compound symmetry is used as the covariance structure.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12, 24, 36, and 48

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	41[9]			
Units: kg				
least squares mean (confidence interval 95%)				
Week 12	0.80 (-0.12 to 1.73)			
Week 24	1.35 (0.36 to 2.33)			
Week 36	2.05 (0.52 to 3.58)			
Week 48	2.45 (0.01 to 4.88)			

Notes:

[9] - P-values: Week 12=0.0872; Week 24=0.0073; Week 36=0.0086; Week 48=0.0489

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in HHD Raw Strength (Key Pinch) Over Time

End point title	Change From Baseline in HHD Raw Strength (Key Pinch) Over Time

End point description:

The highest force value collected using hand held dynamometer for each muscle group was used for data analysis.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12, 24, 36, and 48

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	41[10]			
Units: kg				
arithmetic mean (standard deviation)				
Week 12; n=41	0.110 (± 0.7083)			
Week 24; n=30	0.112 (± 0.6534)			
Week 36; n=23	0.049 (± 0.8090)			

Week 48; n=11	0.318 (± 0.9509)			

Notes:

[10] - n=number of subjects with a baseline and post-baseline assessment at given time point

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 48 Weeks (plus 30 [+5] days for participants not enrolling in extension study)	
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	

Serious adverse events	Ace-ER 6 g/day		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 42 (2.38%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pyelonephritis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 42 (2.38%)		
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	26 / 42 (61.90%)		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	4 / 42 (9.52%)		
occurrences (all)	10		
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	4		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	7		
Oedema peripheral			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	4		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	7 / 42 (16.67%)		
occurrences (all)	9		
Abdominal pain upper			
subjects affected / exposed	6 / 42 (14.29%)		
occurrences (all)	7		
Dyspepsia			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	3		
Dysphagia			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	3		
Flatulence			
subjects affected / exposed	7 / 42 (16.67%)		
occurrences (all)	12		
Nausea			

subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	4		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	3		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	5		
Back pain			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	6		
Muscular weakness			
subjects affected / exposed	4 / 42 (9.52%)		
occurrences (all)	4		
Pain in extremity			
subjects affected / exposed	4 / 42 (9.52%)		
occurrences (all)	6		
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	7 / 42 (16.67%)		
occurrences (all)	7		
Urinary tract infection			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	8		
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 March 2017	The UX0001-CL203 Original Protocol (dated 04 December 2015) has been modified by Amendment 1 to: a) increase the planned number of enrolled subjects; b) clarify the timing and conduct of the Safety Follow-up Period for all subjects; c) clarify that study assessments for a subject should be performed in a consistent order at each visit; d) add urine microscopic examination if abnormal urinalysis results are observed; e) update information regarding safety laboratory blood and urine sample collection and the analytes to be assessed in the samples; f) instruct that the Short Form Health Survey-36 (SF-36) will only be completed for subjects when a validated version is available in the subject's native language; g) remove the requirement for urine collection for assessment of sialic acid (SA), h) update the requirement for urine collection for N-acetyl-D-mannosamine (ManNAc); i) clarify safety reporting requirements; j) more clearly define the various study period/visits and the associated assessments; k) remove reference to the Study Reference Manual; l) clarify what will be done with leftover blood and urine samples from this study; m) correct the volume of blood to be drawn from subjects; n) correct inconsistencies between sections; o) update the retention requirement for subject identifiers, subject files, and other source data; p) update the Sponsor's Responsible Medical Officer information; q) add the designated Coordinating Investigator.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported