Clinical trial results:
An Open-Label Phase 2 Study to Assess Safety and Clinical Effects of UX007 in Subjects with Long-Chain Fatty Acid Oxidation Disorders (LC-FAOD)

Summary

EudraCT number	2013-004830-14
Trial protocol	GB
Global end of trial date	25 August 2016

Results information

Result version number	v1
This version publication date	22 October 2017
First version publication date	22 October 2017

Trial information

Trial identification

Sponsor protocol code	UX007-CL201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01886378
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ultragenyx Pharmaceutical Inc.
Sponsor organisation address	60 Leveroni Court, Novato, California, United States, 94949
Public contact	Kim Mooney, Ultragenyx Pharmaceutical Inc., 1 4154838813, kmooney@ultragenyx.com
Scientific contact	UX007 Medical Monitor, Ultragenyx Pharmaceutical Inc. , 1 4154838800,

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	25 August 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 August 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate the impact of UX007 on acute clinical pathophysiology associated with long-chain fatty acid oxidation disorders (LC-FAOD) following 24 weeks of treatment.

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	06 February 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	United States: 25
Worldwide total number of subjects	29
EEA total number of subjects	4

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)	5
Children (2-11 years)	12
Adolescents (12-17 years)	4
Adults (18-64 years)	8
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Following the signing of informed consent at the Screening visit, each subject continued on current LC-FAOD management for a 4-week Run-in Period to establish a clinical baseline. Following completion of the 4-week Run-in Period, subjects discontinued any use of medium chain triglycerides (MCT) and began treatment with UX007.

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	UX007

Arm description:

UX007 dosing was titrated to a target dose of 25-35% of total caloric intake or maximum tolerated dose. Subjects were followed to evaluate the effects of UX007 over 24 weeks (Treatment Period), then continued treatment in the Extension Period for an additional 54 weeks for a total of 78 weeks of treatment.

Arm type	Experimental
Investigational medicinal product name	triheptanoin
Investigational medicinal product code	UX007
Other name	
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use

Dosage and administration details:

UX007 was administered orally (PO) mixed into food or drink (including formula) or by gastrostomy tube at least four times per day (breakfast, lunch, dinner, and before bed), titrated up to a target dose comprising up to 25-35% of total calories or maximum tolerated dose. The total daily dose may have been divided into smaller, more frequent doses and mixed with food or drink (including formula) as needed, as indicated in the administration guideline.

Number of subjects in period 1	UX007
Started	29
Completed 24 weeks of UX007 treatment	25
Completed	24
Not completed	5
Consent withdrawn by subject	4
Adverse event	1

Baseline characteristics

Reporting groups	
Reporting group title	UX007

Reporting group description:

UX007 dosing was titrated to a target dose of 25-35% of total caloric intake or maximum tolerated dose. Subjects were followed to evaluate the effects of UX007 over 24 weeks (Treatment Period), then continued treatment in the Extension Period for an additional 54 weeks for a total of 78 weeks of treatment.

Reporting group values	UX007	Total	
Number of subjects	29	29	
Age categorical Units: Subjects			
0 - 1 years	2	2	
> 1 - 6 years	13	13	
> 6 -18 years	8	8	
> 18 years	6	6	
Age continuous Units: years			
arithmetic mean	12.06		
standard deviation	± 5.26	-	
Gender categorical Units: Subjects			
Female	12	12	
Male	17	17	

End points

End points reporting groups

Reporting group title	UX007

Reporting group description:

UX007 dosing was titrated to a target dose of 25-35% of total caloric intake or maximum tolerated dose. Subjects were followed to evaluate the effects of UX007 over 24 weeks (Treatment Period), then continued treatment in the Extension Period for an additional 54 weeks for a total of 78 weeks of treatment.

Subject analysis set title	Primary Analysis Set – Cycle Ergometry
Subject analysis set type	Full analysis

Subject analysis set description:

The primary analysis set – Cycle Ergometry is the subset of subjects in the primary analysis set who had at least one cycle ergometry test performed with any duration.

Subject analysis set title	Primary Analysis Set – 12MWT
Subject analysis set type	Full analysis

Subject analysis set description:

The primary analysis set – 12MWT is the subset of subjects in the primary analysis set who had at least one 12MWT performed with any distance walked.

Subject analysis set title	Primary Analysis Set – SF-10
Subject analysis set type	Full analysis

Subject analysis set description:

The primary analysis set – SF-10 is the subset of subjects in the primary analysis set who had at least one SF-10 test performed.

Subject analysis set title	Primary Analysis Set – SF-12
Subject analysis set type	Full analysis

Subject analysis set description:

The primary analysis set – SF-12 is the subset of subjects in the primary analysis set who had at least one SF-12 test performed.

Subject analysis set title	Primary Analysis Set
Subject analysis set type	Full analysis

Subject analysis set description:

The primary analysis set is the subset of subjects in the full analysis set who completed the 4-week run-in period and received at least one dose of UX007.

Primary: Change From Baseline in Total Area Under the Curve (AUC) for Workload During Cycle Ergometry at Week 24

End point title	Change From Baseline in Total Area Under the Curve (AUC) for Workload During Cycle Ergometry at Week 24[1]

End point description:

To evaluate the impact 24 weeks of treatment with UX007 has on exercise intolerance, the change from Baseline in total AUC for workload during 40-minute cycle ergometry tests at Week 24 were assessed using the generalized estimation equation (GEE) model. The GEE model included the change from Baseline as the dependent variable, time as the categorical variable, and adjusted for Baseline measurement with compound symmetry covariance structure. An increase in AUC is reflective of improved exercise tolerance; a negative change from Baseline indicates worsening.

End point type	Primary

End point timeframe:

Baseline, Week 24

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: Due to limitations of the EudraCT system, statistical analyses had to be uploaded as an attachment (see zip file below the Endpoint Values table).

End point values	Primary Analysis Set – Cycle Ergometry			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: watts				
least squares mean (standard error)	423.594 (± 295.54)			

Attachments (see zip file)	Statistical Analysis - Cycle Ergometry, Workload.docx

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Time-Adjusted AUC for Respiratory Exchange Ratio (RER) During Cycle Ergometry at Week 24

End point title	Change From Baseline in Time-Adjusted AUC for Respiratory Exchange Ratio (RER) During Cycle Ergometry at Week 24[2]

End point description:

To evaluate the impact 24 weeks of treatment with UX007 has on exercise intolerance, the change from Baseline in time-adjusted AUC for RER during cycle ergometry at Week 24 was assessed using the GEE model. The GEE model included the change from Baseline as the dependent variable, time as the categorical variable, and adjusted for Baseline measurement with compound symmetry covariance structure.

End point type	Primary

End point timeframe:

Baseline, Week 24

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to limitations of the EudraCT system, statistical analyses had to be uploaded as an attachment (see zip file below the Endpoint Values table).

End point values	Primary Analysis Set – Cycle Ergometry			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: ratio				
least squares mean (standard error)	-0.011 (± 0.0132)			

Attachments (see zip file)	Statistical Analysis - Cycle Ergometry, RER.docx

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Actual Duration of Exercise During Cycle Ergometry at Week 24

End point title	Change From Baseline in Actual Duration of Exercise During Cycle Ergometry at Week 24[3]

End point description:

To evaluate the impact of 24 weeks of treatment with UX007 on exercise intolerance, the change from Baseline in actual duration of exercise during 40-minute cycle ergometry tests at Week 24 was assessed using the GEE model. The GEE model included the change from Baseline as the dependent variable, time as the categorical variable, and adjusted for Baseline measurement with compound symmetry covariance structure. Duration of exercise is expected to increase as exercise tolerance improves.

End point type	Primary

End point timeframe:

Baseline, Week 24

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to limitations of the EudraCT system, statistical analyses had to be uploaded as an attachment (see zip file below the Endpoint Values table).

End point values	Primary Analysis Set – Cycle Ergometry			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: minutes				
least squares mean (standard error)	4.671 (± 2.65)			

Attachments (see zip file)	Statistical Analysis - Cycle Ergometry, Duration.docx

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Distance Traveled During the 12-Minute Walk Test (12MWT) at Week 18

End point title	Change From Baseline in Distance Traveled During the 12-Minute Walk Test (12MWT) at Week 18[4]

End point description:

To evaluate the impact 24 weeks of treatment with UX007 has on muscle function, the change from Baseline in distance traveled during a 12MWT at Week 18 was assessed using the GEE model. The GEE model included the change from Baseline as the dependent variable, time as the categorical variable, and adjusted for Baseline measurement with compound symmetry covariance structure.Distance traveled during the 12MWT is expected to increase as muscle function increases.

End point type	Primary

End point timeframe:

Baseline (last assessment during the 4-week run-in period), Week 18

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to limitations of the EudraCT system, statistical analyses had to be uploaded as an attachment (see zip file below the Endpoint Values table).

End point values	Primary Analysis Set – 12MWT			
Subject group type	Subject analysis set			
Number of subjects analysed	8			
Units: beats/meter				
least squares mean (standard error)	181.37 (± 104.63)			

Attachments (see zip file)	Statistical Analysis - 12MWT Parameters 12MWT.docx

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Energy Expenditure Index (EEI) During the 12MWT at Week 18

End point title	Change From Baseline in Energy Expenditure Index (EEI) During the 12MWT at Week 18[5]

End point description:

To evaluate the impact 24 weeks of treatment with UX007 has on muscle function, the change from Baseline of EEI during the 12MWT at Week 18 was assessed using the GEE model. The GEE model included the change from Baseline as the dependent variable, time as the categorical variable, and adjusted for Baseline measurement with compound symmetry covariance structure. EEI during the 12MWT is expected to decrease as walking capacity improves.

End point type	Primary

End point timeframe:

Baseline (last assessment during the 4-week run-in period), Week 18

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to limitations of the EudraCT system, statistical analyses had to be uploaded as an attachment (see zip file below the Endpoint Values table).

End point values	Primary Analysis Set – 12MWT			
Subject group type	Subject analysis set			
Number of subjects analysed	8			
Units: meters				
least squares mean (standard error)	-0.185 (± 0.09)			

Attachments (see zip file)	Statistical Analysis - 12MWT Parameters, EEI.docx

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of the Predicted 6-Minute Walk Test (6MWT) Distance Walked

at Week 18

End point title	Percentage of the Predicted 6-Minute Walk Test (6MWT) Distance Walked at Week 18[6]

End point description:

To evaluate the impact 24 weeks of treatment with UX007 has on muscle function, the change from Baseline in distance traveled during the first 6 minutes of the 12MWT (expressed as a percentage of the predicted 6MWT distance) at Week 18 was assessed using the GEE model. The GEE model included the change from Baseline as the dependent variable, time as the categorical variable, and adjusted for Baseline measurement with compound symmetry covariance structure. Percent predicted values are expected to increase as muscle function increases.

End point type	Primary

End point timeframe:

Baseline (last assessment during the 4-week run-in period), Week 18

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to limitations of the EudraCT system, statistical analyses had to be uploaded as an attachment (see zip file below the Endpoint Values table).

End point values	Primary Analysis Set – 12MWT			
Subject group type	Subject analysis set			
Number of subjects analysed	8			
Units: % predicted				
least squares mean (standard error)	12.44 (± 7.22)			

Attachments (see zip file)	Statistical Analysis - 12MWT Parameters, 6MWT.docx

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Physical Summary Score (PHS-10) of the Short Form 10 (SF10) at Week 24

End point title	Change From Baseline in Physical Summary Score (PHS-10) of the Short Form 10 (SF10) at Week 24[7]

End point description:

To evaluate the impact treatment with UX007 has on functional disability and health in subjects between 5 and 17 years of age, change from Baseline in the T-scores of the PHS-10 were assessed at Week 24 and analyzed using the GEE model. The GEE model included the change from Baseline as the dependent variable, time as the categorical variable, and adjusted for Baseline measurement with compound symmetry covariance structure.

The SF10 Health Survey for Children is a 10-item caregiver-completed assessment designed to measure children's health-related quality of life through questions related to the child's physical wellness, feelings, behavior, and activities at school and with family and friends. The PHS-10 of the SF 10 is scored such that higher scores indicate more favorable functioning.

End point type	Primary

End point timeframe:

Baseline, Week 24

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to limitations of the EudraCT system, statistical analyses had to be uploaded as an attachment (see zip file below the Endpoint Values table).

End point values	Primary Analysis Set – SF-10			
Subject group type	Subject analysis set			
Number of subjects analysed	5			
Units: units on a scale				
least squares mean (standard error)	2.16 (± 2.44)			

Attachments (see zip file)	Statistical Analysis - SF-10 Physical Summary Score.docx

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Psychosocial Summary Score (PSS-10) of the SF10 at Week 24

End point title	Change From Baseline in Psychosocial Summary Score (PSS-10) of the SF10 at Week 24[8]

End point description:

To evaluate the impact treatment with UX007 has on functional disability and health in subjects between 5 and 17 years of age, changes from Baseline in the T-scores of the PSS-10 were assessed at Week 24 and analyzed using the GEE model. The GEE model included the change from Baseline as the dependent variable, time as the categorical variable, and adjusted for Baseline measurement with compound symmetry covariance structure.

The SF10 Health Survey for Children is a 10-item caregiver-completed assessment designed to measure children's health-related quality of life through questions related to the child's physical wellness, feelings, behavior, and activities at school and with family and friends. The PSS-10 of the SF10 is scored such that higher scores indicate more favorable functioning.

End point type	Primary

End point timeframe:

Baseline, Week 24

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to limitations of the EudraCT system, statistical analyses had to be uploaded as an attachment (see zip file below the Endpoint Values table).

End point values	Primary Analysis Set – SF-10			
Subject group type	Subject analysis set			
Number of subjects analysed	5			
Units: units on a scale				
least squares mean (standard error)	0.816 (± 2.63)			

Attachments (see zip file)	Statistical Analysis - SF-10 Psychosocial Summary Score.docx

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in the Physical Component Summary Scale (PCS-12) at Week 24

End point title	Change From Baseline in the Physical Component Summary Scale (PCS-12) at Week 24[9]

End point description:

Changes from baseline in T-scores as assessed by the PCS-12 Short-Form Health Survey, version 2 (SF-12v2) at Week 24 were assessed using the GEE model. The GEE model included the change from Baseline as the dependent variable, time as the categorical variable, and adjusted for Baseline measurement with compound symmetry covariance structure.

The 12-item SF-12v2 has several brief broad questions on 8 aspects of health (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health) that the subject was asked to score over the last week. The PCS-12 scores were calculated from the individual responses to those questions contribute to physical health. A higher score indicates a better subject perceived state of health. All domains were scored on a scale from 0 (lowest health state) to 100 (highest health state).

End point type	Primary

End point timeframe:

Baseline, Week 24

Notes:

[9] - 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: Due to limitations of the EudraCT system, statistical analyses had to be uploaded as an attachment (see zip file below the Endpoint Values table).

End point values	Primary Analysis Set – SF-12			
Subject group type	Subject analysis set			
Number of subjects analysed	5			
Units: units on a scale				
least squares mean (standard error)	8.88 (± 1.63)			

Attachments (see zip file)	Statistical Analysis - SF-12 Physical Summary Score.docx

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in the Mental Component Summary Scale (MCS-12) at Week 24

End point title	Change From Baseline in the Mental Component Summary Scale (MCS-12) at Week 24[10]

End point description:

To evaluate the impact treatment with UX007 has on functional disability and health in participants ≥ 18 years of age, the changes from baseline of T-scores as assessed by the MCS-12 of the SF-12v2 at Week 24 were assessed using the GEE model. The GEE model included the change from Baseline as the dependent variable, time as the categorical variable, and adjusted for Baseline measurement with compound symmetry covariance structure.

The SF-12v2 has several brief broad questions on 8 aspects of health (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health) that the subject was asked to score over the last week. The MCS-12 scores were calculated from the individual responses to those questions contributing to mental health. A higher score indicates a better subject perceived state of health. All domains were scored on a scale from 0 (lowest health state) to 100 (highest health state).

End point type	Primary

End point timeframe:

Baseline, Week 24

Notes:

[10] - 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: Due to limitations of the EudraCT system, statistical analyses had to be uploaded as an attachment (see zip file below the Endpoint Values table).

End point values	Primary Analysis Set – SF-12			
Subject group type	Subject analysis set			
Number of subjects analysed	5			
Units: units on a scale				
least squares mean (standard error)	9.7 (± 4)			

Attachments (see zip file)	Statistical Analysis - SF-12 Mental Summary Score.docx

Statistical analyses

No statistical analyses for this end point

Primary: Annualized Event Rate of All Major Clinical Events Pre- and Post-Treatment with UX007

End point title	Annualized Event Rate of All Major Clinical Events Pre- and Post-Treatment with UX007[11]

End point description:

Major clinical events are defined as adverse events (AEs) resulting in hospitalizations, emergency room (ER) visits, and emergency intervention.

End point type	Primary

End point timeframe:

18 months before and after UX007 initiation

Notes:

[11] - 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	Primary Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	29			
Units: events/year				
arithmetic mean (standard deviation)				
Pre-UX007	1.69 (± 1.6081)			
Post-UX007	0.877 (± 1.142)			

Statistical analyses

No statistical analyses for this end point

Primary: Annualized Duration Rate of All Major Clinical Events Pre- and Post-Treatment with UX007

End point title	Annualized Duration Rate of All Major Clinical Events Pre- and Post-Treatment with UX007[12]

End point description:

Major clinical events are defined as AEs resulting in hospitalizations, ER visits, and emergency intervention.

End point type	Primary

End point timeframe:

18 months before and after UX007 initiation

Notes:

[12] - 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	Primary Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	29			
Units: days/year				
arithmetic mean (standard deviation)				
Pre-UX007	5.961 (± 6.0783)			
Post-UX007	2.964 (± 3.9733)			

Statistical analyses

No statistical analyses for this end point

Primary: Annualized Event Rate of Major Rhabdomyolysis Clinical Events Pre- and Post-Treatment with UX007

End point title	Annualized Event Rate of Major Rhabdomyolysis Clinical Events Pre- and Post-Treatment with UX007[13]

End point description:

Rhabdomyolysis is a condition in which damaged skeletal muscle breaks down rapidly. Major rhabdomyolysis clinical events are defined as those AEs resulting in hospitalizations, ER visits, and emergency intervention.

End point type	Primary

End point timeframe:

18 months before and after UX007 initiation

Notes:

[13] - 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	Primary Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	29			
Units: events/year				
arithmetic mean (standard deviation)				
Pre-UX007	1.303 (± 1.5007)			
Post-UX007	0.833 (± 1.1513)			

Statistical analyses

No statistical analyses for this end point

Primary: Annualized Duration Rate of Major Rhabdomyolysis Clinical Events Pre- and Post-Treatment with UX007

End point title	Annualized Duration Rate of Major Rhabdomyolysis Clinical Events Pre- and Post-Treatment with UX007[14]

End point description:

Rhabdomyolysis is a condition in which damaged skeletal muscle breaks down rapidly. Major rhabdomyolysis clinical events are defined as those AEs resulting in hospitalizations, ER visits, and emergency intervention.

End point type	Primary

End point timeframe:

18 months before and after UX007 initiation

Notes:

[14] - 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	Primary Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	29			
Units: days/year				
arithmetic mean (standard deviation)				
Pre-UX007	3.949 (± 4.3687)			
Post-UX007	2.792 (± 3.8452)			

Statistical analyses

No statistical analyses for this end point

Primary: Annualized Event Rate of Major Hypoglycemia Clinical Events Pre- and Post-Treatment with UX007

End point title	Annualized Event Rate of Major Hypoglycemia Clinical Events Pre- and Post-Treatment with UX007[15]

End point description:

Major hypoglycemia clinical events are defined as those AEs resulting in hospitalizations, ER visits, and emergency intervention.

End point type	Primary

End point timeframe:

18 months before and after UX007 initiation

Notes:

[15] - 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	Primary Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	29			
Units: events/year				
arithmetic mean (standard deviation)				
Pre-UX007	0.318 (± 0.9053)			
Post-UX007	0.023 (± 0.1224)			

Statistical analyses

No statistical analyses for this end point

Primary: Annualized Duration Rate of Major Hypoglycemia Clinical Events Pre- and Post-Treatment with UX007

End point title	Annualized Duration Rate of Major Hypoglycemia Clinical Events Pre- and Post-Treatment with UX007[16]

End point description:

Major hypoglycemia clinical events are defined as those AEs resulting in hospitalizations, ER visits, and emergency intervention.

End point type	Primary

End point timeframe:

18 months before and after UX007 initiation

Notes:

[16] - 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	Primary Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	29			
Units: days/year				
arithmetic mean (standard deviation)				
Pre-UX007	1.414 (± 4.3025)			
Post-UX007	0.023 (± 0.1224)			

Statistical analyses

No statistical analyses for this end point

Primary: Annualized Event Rate of Major Cardiac Clinical Events Pre- and Post-Treatment with UX007

End point title	Annualized Event Rate of Major Cardiac Clinical Events Pre- and Post-Treatment with UX007[17]

End point description:

Major cardiac clinical events are defined as those AEs resulting in hospitalizations, ER visits, and emergency intervention.

End point type	Primary

End point timeframe:

18 months before and after UX007 initiation

Notes:

[17] - 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	Primary Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	29			
Units: events/year				
arithmetic mean (standard deviation)				
Pre-UX007	0.069 (± 0.2728)			
Post-UX007	0.021 (± 0.115)			

Statistical analyses

No statistical analyses for this end point

Primary: Annualized Duration Rate of Major Cardiac Clinical Events Pre- and Post-Treatment with UX007

End point title	Annualized Duration Rate of Major Cardiac Clinical Events Pre- and Post-Treatment with UX007[18]

End point description:

Major cardiac clinical events are defined as those AEs resulting in hospitalizations, ER visits, and emergency intervention.

End point type	Primary

End point timeframe:

18 months before and after UX007 initiation

Notes:

[18] - 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	Primary Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	29			
Units: days/year				
arithmetic mean (standard deviation)				
Pre-UX007	0.598 (± 2.4054)			
Post-UX007	0.149 (± 0.8047)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded from the time the subject signed the informed consent through the Follow-up visit (Week 82) or 30 days following the last UX007 administration.

Adverse event reporting additional description:

Events presented are treatment-emergent. An event was considered as treatment-emergent if it occurred on or after the date of the first treatment of UX007.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	UX007

Reporting group description:

UX007 dosing was titrated to a target dose of 25-35% of total caloric intake or maximum tolerated dose. Subjects were followed to evaluate the effects of UX007 over 24 weeks (Treatment Period), then continued treatment in the Extension Period for an additional 54 weeks for a total of 78 weeks of treatment.

Serious adverse events	UX007		
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 29 (65.52%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Congenital, familial and genetic disorders			
Talipes			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiomyopathy Acute			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Infection Prophylaxis			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Gastrointestinal disorders			
Gastrointestinal Disorder			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal Haemorrhage			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Rhabdomyolysis			
subjects affected / exposed	11 / 29 (37.93%)		
occurrences causally related to treatment / all	0 / 26		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	6 / 29 (20.69%)		
occurrences causally related to treatment / all	1 / 6		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis Viral			

subjects affected / exposed	6 / 29 (20.69%)		
occurrences causally related to treatment / all	0 / 9		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal Viral Infection			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Upper Respiratory Tract Infection			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Adenoviral Upper Respiratory Infection			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Adenovirus Infection			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Conjunctivitis			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Coxsackie Viral Infection			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Croup Infectious			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Otitis Media			

subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Otitis Media Acute			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia Mycoplasmal			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory Tract Infection Viral			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Roseola			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary Tract Infection			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Metabolic Disorder			
subjects affected / exposed	1 / 29 (3.45%)		
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	UX007		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 29 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic Naevus			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	9 / 29 (31.03%)		
occurrences (all)	12		
Pain			
subjects affected / exposed	3 / 29 (10.34%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 29 (13.79%)		
occurrences (all)	6		
Nasal Congestion			
subjects affected / exposed	3 / 29 (10.34%)		
occurrences (all)	3		
Oropharyngeal Pain			
subjects affected / exposed	3 / 29 (10.34%)		
occurrences (all)	3		
Rhinorrhoea			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Sinus Congestion			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	4		
Psychiatric disorders			
Anxiety			

subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Irritability			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Panic Attack			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Investigations			
Blood Creatine Phosphokinase Increased			
subjects affected / exposed	3 / 29 (10.34%)		
occurrences (all)	3		
Carnitine Decreased			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Injury, poisoning and procedural complications			
Arthropod Bite			
subjects affected / exposed	3 / 29 (10.34%)		
occurrences (all)	4		
Fall			
subjects affected / exposed	3 / 29 (10.34%)		
occurrences (all)	3		
Laceration			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Procedural Pain			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Stoma Site Pain			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	3		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Nervous system disorders			

Headache			
subjects affected / exposed	9 / 29 (31.03%)		
occurrences (all)	13		
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Eye disorders			
Eye Swelling			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	3		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	16 / 29 (55.17%)		
occurrences (all)	42		
Vomiting			
subjects affected / exposed	13 / 29 (44.83%)		
occurrences (all)	22		
Abdominal Pain			
subjects affected / exposed	8 / 29 (27.59%)		
occurrences (all)	14		
Abdominal Pain Upper			
subjects affected / exposed	4 / 29 (13.79%)		
occurrences (all)	12		
Gastrointestinal Pain			
subjects affected / exposed	3 / 29 (10.34%)		
occurrences (all)	6		
Gastrooesophageal Reflux Disease			
subjects affected / exposed	3 / 29 (10.34%)		
occurrences (all)	3		
Abdominal Distension			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Constipation			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	4		
Flatulence			

subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	4		
Nausea			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	5		
Teething			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	3 / 29 (10.34%)		
occurrences (all)	4		
Dermatitis Allergic			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Rhabdomyolysis			
subjects affected / exposed	8 / 29 (27.59%)		
occurrences (all)	10		
Myalgia			
subjects affected / exposed	5 / 29 (17.24%)		
occurrences (all)	5		
Arthralgia			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	3		
Muscle Spasms			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	3		
Infections and infestations			
Upper Respiratory Tract Infection			
subjects affected / exposed	11 / 29 (37.93%)		
occurrences (all)	32		
Ear Infection			
subjects affected / exposed	5 / 29 (17.24%)		
occurrences (all)	6		
Nasopharyngitis			

subjects affected / exposed	5 / 29 (17.24%)			
occurrences (all)	11			
Bronchitis				
subjects affected / exposed	4 / 29 (13.79%)			
occurrences (all)	4			
Gastroenteritis Viral				
subjects affected / exposed	4 / 29 (13.79%)			
occurrences (all)	6			
Gastrointestinal Viral Infection				
subjects affected / exposed	4 / 29 (13.79%)			
occurrences (all)	4			
Rhinitis				
subjects affected / exposed	4 / 29 (13.79%)			
occurrences (all)	15			
Viral Upper Respiratory Tract Infection				
subjects affected / exposed	4 / 29 (13.79%)			
occurrences (all)	5			
Conjunctivitis				
subjects affected / exposed	3 / 29 (10.34%)			
occurrences (all)	3			
Gastroenteritis				
subjects affected / exposed	3 / 29 (10.34%)			
occurrences (all)	6			
Sinusitis				
subjects affected / exposed	3 / 29 (10.34%)			
occurrences (all)	4			
Urinary Tract Infection				
subjects affected / exposed	3 / 29 (10.34%)			
occurrences (all)	3			
Otitis Media				
subjects affected / exposed	2 / 29 (6.90%)			
occurrences (all)	2			
Respiratory Tract Infection Viral				
subjects affected / exposed	2 / 29 (6.90%)			
occurrences (all)	2			

Metabolism and nutrition disorders Decreased Appetite subjects affected / exposed occurrences (all) Dehydration subjects affected / exposed occurrences (all)	 4 / 29 (13.79%) 4 2 / 29 (6.90%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 November 2013	The changes affecting the conduct of the study are summarized below. 1. The number of study sites increased to approximately 8 sites globally to allow for additional enrollment. 2. The number of subjects planned increased from 20 to 30. 3. The study population was expanded to include a cohort of subjects aged 6 months – 6 years of age. The upper age limit for the study was increased to 35 years of age. 4. The inclusion criteria were modified to include the following: • Male or female, 6 months –35 years of age • Willing and able to provide access to medical records charting the last 18-24 months of care prior to the study initiation, or from birth for those subjects less than 18 months of age • Have severe LC-FAOD, as evidenced by ANY ONE of the following significant clinical manifestations despite management: Episodic Elevated creatine kinase (CK) with Reported Muscle Dysfunction: Episodes of elevated CK levels over the last 6 months -1 year (defined as ≥ 2X upper limit of age/gender-matched normal, or ≥ 500 units/L if age-matched reference is not established), AND patient report of frequent muscle pain and muscle fatigue, exercise intolerance, or limitation of • Frequent Severe Major Medical Episodes (at least 3 within the past year, or 5 within 2 years) of hypoglycemia, rhabdomyolysis, or exacerbation of cardiomyopathy (CM), requiring ER/acute care visits or hospitalizations 5. Specific language regarding stopping rules was modified to remove language suspending enrollment if two subjects develop the same Grade 3 AE that is unexpected and possibly, probably, or definitely related to study drug, or if any subject develops a Grade 4 AE that is unexpected and possible, probably, or definitely related to study drug. 6. The requirement for subjects to return all unused study drug, and for site personnel to estimate the remaining volume of unused medication, was removed.
04 November 2013	(continued) 7. To specify procedures and age-specific assessments in subjects < 6 years of age, an additional Schedule of Events (Table 2.2: Schedule of Events for Subjects < 6 years of Age) was inserted. An additional assessment of growth was obtained at the Screening Visit. The Pediatric Evaluation of Disability Inventory-Computer Adaptive Test (PEDI-CAT), SF-10/SF-12 assessments at the Screening Visit were unnecessary and removed. 8. Skeletal Myopathy Efficacy Measures were modified as follows: • Exercise Intolerance. During cycle ergometry, additional monitoring of blood pressure, pain and perceived exertion, and biochemical markers will be conducted as specified in the Clinical Evaluator's Manual. The OMNI scale will be used in place of the Borg scale to measure perceived exertion. The Faces Pain Scale – Revised (or visual analog scale) will be used as an age-appropriate measure of perceived muscle pain. The requirement for the dose and standard macronutrient meal 2 hours prior to cycle ergometry has been relaxed to "approximately 2 hours". Subjects will be fed a standardized macronutrient meal including either MCT (at the Screening and Baseline Visits, if applicable) or UX007 (all visits post-Baseline), approximately 2 hours prior to test administration. Subjects and/or caregivers will report activity level in the electronic diary at each incidence of muscle pain/leg cramps and muscle weakness/fatigue. Subjects and/or caregivers will report the number of episodes or events of muscle pain and leg cramps on exertion in the electronic diary on a daily basis.

04 November 2013	(#8, continued) • Muscle Function and Motor Development. Subjects will be required to consume study drug (or MCT during the Run-in period, if applicable) and a standard macronutrient meal approximately 2 hours prior to the 12MWT. The OMNI scale will be used in place of the Borg scale to measure perceived exertion. The Faces Pain Scale (subjects < 18 years) or visual analog scale (subjects ≥ 18 years) will be used to measure perceived muscle pain. Respiratory rate has been removed as an assessment during the 12MWT. Subjects < 6 years of age will not perform the 12MWT. The Peabody Developmental Motor Scales – 2nd Edition (PDMS-2) has been added as an age-appropriate measure of gross motor development in subjects < 6 years of age. Subjects will be required to consume study drug and a standard macronutrient meal approximately 2 hours prior to testing with the PDMS-2. 9. LC-FAOD Laboratory Measures were modified as follows: • An additional serum sample, designated for exploratory biomarker research, will be collected at the Baseline and Week 24 visits. • Inflammatory cytokines will not be specifically assessed, but may be investigated as part of the additional research sample. • Plasma heptanoate will be assessed as a pharmacokinetic (PK) metabolite 10. An additional measurement of head circumference was included as a growth parameter in subjects aged ≤ 36 months at each visit. 11. Acceptable methods of contraception, including abstinence, were specified for females and males of childbearing potential. 12. Additional safety monitoring calls were included within 36 hours following the completion of each 12MWT, and within 36 hours of any cycle ergometer test not associated with post-test blood to assess AEs related to the 12MWT or cycle ergometer test. 13. The 3-day diet history was modified as a paper diary (previously electronic). The requirement to maintain a 3-day diet history following any dose-adjustment was deleted.
04 November 2013	(continued) 14. Additional information on electronic diary data capture was added. 15. Contact information for calls related to serious AEs was provided for BioSoteria, the Medical Monitor.
20 February 2014	The changes affecting the conduct of the study are summarized below. 1. The study population was expanded to include subjects diagnosed with trifunctional protein (TFP) deficiency. The Inclusion and Exclusion Criteria were modified to reflect this change. 2. Subjects were required to consume study drug (or MCT at the Baseline visit, if applicable) and a standard macronutrient meal approximately 2 hours prior to the PDMS-2 test to assess subjects in the post-absorptive state. 3. Fasting serum glucose collection was specified after a 4 hour fast, or as tolerated by subjects at the discretion of the PI. 4. Blood sample collection for PK of UX007 and UX007 metabolites was specified for 2-hours after a standardized macronutrient meal including either MCT (at Run-in or Baseline, if applicable) or UX007 (all visits post-Baseline).

13 May 2014	The changes affecting the conduct of the study are summarized below. 1. The number of study sites was increased to approximately 10 sites globally to support enrollment. 2. The study population was expanded to included subject over age 35. The upper age limit for the study was removed from the Inclusion Criteria. 3. Additional chronic toxicity studies in mini-pigs was added to the nonclinical summary. 4. Subjects who will reach 6 years old within 6 months of the Baseline visit were added for consideration for the cycle ergometry assessments. 5. The criteria for the 12MWT were expanded to include subjects who reach 6 years old during the study or achieve mastery of all PDMS-2 skill sets. 6. In order to minimize patient burden, additional language was placed to specify that the Clinical Evaluator, Investigator, and Sponsor would assess the requirement of additional PDMS-2 assessments during the study for those subjects that have already demonstrated a mastery of the skills that are being measured. 7. The description of the Data Monitoring Committee was clarified.
03 February 2016	The changes affecting the conduct of the study are summarized below. 1. Pancreatic lipase inhibitors were added to the list of prohibited medications following in vitro studies demonstrating that pancreatic lipases hydrolyze triheptanoin. Oral salicylates were removed from the list of prohibited medications. 2. The use of electronic diaries was discontinued due to unexpected performance issues. Paper diaries replaced the electronic diaries and captured the same data; therefore, references to electronic diary use were removed. 3. Interim analysis at Week 48 was removed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28189603