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)

Protocol Number: **UX001-CL302**

Original Protocol: **10 February 2016**

Amendment 1: **17 June 2016**

Investigational Product:	Aceneuramic Acid Extended-Release (Ace-ER) Tablets
Indication:	Treatment of GNE myopathy (GNEM), also known as hereditary inclusion body myopathy (HIBM), distal myopathy with rimmed vacuoles (DMRV), or Nonaka disease
IND/EudraCT Number:	109,334 / 2016-000360-42
Sponsor:	Ultragenyx Pharmaceutical Inc. 60 Leveroni Court Novato, CA 94949 USA
Sponsor's Responsible Medical Officer:	Ed Conner, MD Vice President, Clinical Science PPD
Coordinating Investigator:	TBD

This study is to be performed in compliance with the protocol, Good Clinical Practices (GCP), and applicable regulatory requirements.

CLINICAL STUDY PROTOCOL AMENDMENT

SUMMARY OF CHANGES AND RATIONALE

UX001-CL302 Amendment 1

17 June 2016

The original protocol of UX001-CL302 (dated 10 Feb 2016) has been modified by Amendment 1 to incorporate a number of changes based on additional information acquired since the beginning of the study. The major changes to the protocol impacting the conduct of the study are summarized below. Additional changes have also been made to provide supportive background information and rationale for the proposed changes (along with minor edits for consistency and clarity) but are not detailed in this summary.

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.

   Rationale: This change was made to provide subjects in UX001-CL202 an opportunity to continue treatment with Ace-ER (6 g/day) and obtain long-term safety and efficacy data in UX001-CL302.

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.

   Rationale: Evaluations of Ace-ER in patients with GNEM have shown that the 6 g/day is the optimal dose. Clinical efficacy with 6 g/day surpassed the 3 g/day dose and 12 g/day did not appear to confer additional benefit beyond that observed with 6 g/day, with an increase in GI disturbance, most notably flatulence.

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.

   Rationale: This change was made to incorporate feedback from MHRA in order to clarify end of study.

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.

Rationale: The change was made to clarify the analytes that will be tested in urinalysis and confirm that microscopic evaluation will be conducted for abnormal 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.

   Rationale: This added text will ensure the safety of subjects who rollover from the UX001-CL202 study and are unable to perform an assessment due to disease progression.

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.

   Rationale: The change was made to clarify the total blood volume required to ensure a primary and back-up serum sialic acid sample are obtained and also to clarify the total volume of blood to be obtained during the study.

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.

   Rationale: This administrative change has been made to reflect upcoming changes to EU clinical trial regulations and current regulations by other health authorities.

2 SYNOPSIS

TITLE OF STUDY:

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)

PROTOCOL NUMBER:

UX001-CL302

STUDY SITES:

Approximately 15 sites, globally

PHASE OF DEVELOPMENT:

Phase 3b

RATIONALE:

GNEM (or HIBM), is a severe, progressive myopathy caused by a defect in the biosynthetic pathway for sialic acid (SA). Substrate replacement is a potential therapeutic strategy based on the success of replacing missing SA and reducing muscle disease in a relevant mouse model of the human disease. Successful use of SA replacement therapy in humans is believed to depend upon providing steady, long-term exposure to the compound in an extended-release form (such as Ace-ER), given SA's short half-life. A Phase 2, placebo-controlled study evaluating Ace-ER at 2 doses for 48 weeks (UX001-CL201) found that the higher dose of 6 g/day Ace-ER stabilized a composite of upper extremity muscle strength (UEC score) compared with placebo or the lower 3 g/day dose; this finding was supported by improvements in functional outcome on the GNE Myopathy Functional Activities Scale (GNEM-FAS). This Phase 3b extension study will assess the long-term safety of Ace-ER in patients who participated in and completed the UX001-CL202, UX001-CL301, or UX001-CL203 studies; in addition, efficacy of 6 g/day Ace-ER will be further evaluated in GNEM patients, including those able to walk ≥200 m in the 6-minute walk test (6MWT) (roll over subjects from UX001-CL301 and naïve subjects from UX001-CL202) and GNEM patients with severe ambulatory impairment (roll over subjects from UX001-CL203).

OBJECTIVE:

- To evaluate the long-term safety and efficacy of Ace-ER treatment of GNE Myopathy subjects

ENDPOINTS:

Overall Safety Endpoint (Primary Endpoint): Evaluate the long-term safety of 6 g/day Ace-ER treatment in subjects with GNE Myopathy

Overall Efficacy Endpoints: Evaluate the long-term effect of 6 g/day of Ace-ER treatment in subjects with GNEM. Efficacy will be evaluated as follows:

For Subjects Enrolling from UX001-CL202 and UX001-CL301:

- Muscle strength as measured by dynamometry
- Mobility, strength, and function using a series of physical performance measures
- Functional disability using an patient- and clinician-reported questionnaire

For Subjects Enrolling from UX001-CL203:

- Change in GNEM-FAS Expanded Version total score and mobility, upper extremity and self-care domain scores
- Change in upper extremity strength in grip, key pinch, shoulder abductors and wrist extensors and in lower extremity muscle strength in the knee extensors as measured by dynamometry
- Evaluate the effect on 6g/day Ace-ER on health-related quality of life (HRQoL), patient reported outcomes (PRO), and biomarkers of sialyation

STUDY DESIGN AND METHODOLOGY:

This open-label extension study of Ace-ER will assess the long-term safety and efficacy of Ace-ER treatment over a period of 24 months. Approximately 165 subjects from the UX001-CL202, UX001-CL301, and UX001-CL203 studies will be eligible to enroll in the study.

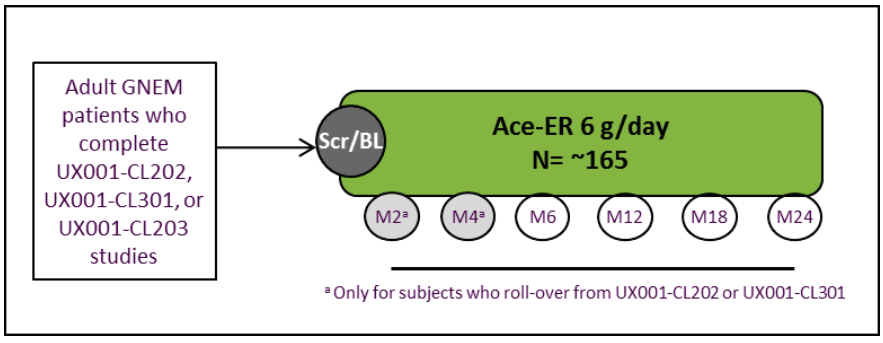
Subjects will take 4 tablets (500 mg Ace-ER each for 2 g per dose) orally 3 times per day (TID). The dose should be taken with food (i.e. within 30 minutes after a meal or snack). Subjects being treated with 12 g/day Ace-ER in UX001-CL202 will be transitioned to the 6 g/day Ace-ER dose in this protocol. Treatment will be administered for a total of 24 months. Study visits will occur every 8 weeks for 24 weeks and then every 6 months for subjects enrolling from UX001-CL202 or UX001-CL301. For subjects enrolling from the UX001-CL203 study, study visits will occur every 6 months. Assessments will be performed as outlined in the Schedule of Events (Table 2.1).

Safety will be evaluated by review of the incidence and frequency of AEs and SAEs and clinically significant changes in interval history, physical examination results, vital signs, clinical laboratory test results, the Columbia Suicide Severity Rating Scale (C-SSRS), and concomitant medications.

Blood samples will be collected to evaluate biomarkers (for example sialylation of serum proteins before and after treatment) to determine their utility in predicting clinical outcomes.

Efficacy will be evaluated based on assessments used in the parent study from which subjects roll over (subjects enrolling from UX001-CL202 will follow the same schedule of events as subjects who roll over from UX001-CL301), and include dynamometry as a measure of muscle strength and patient- and clinician-reported outcome measures as indicators of physical functioning and quality of life. Figure 2.1 provides a schematic of the study design.

Figure 2.1: Study Schema



NUMBER OF SUBJECTS PLANNED:

Approximately 165 adult subjects with GNEM are expected to roll-over from the UX001-CL202, UX001-CL301 or UX001-CL203 studies to participate in this extension study.

DIAGNOSIS AND CRITERIA FOR INCLUSION AND EXCLUSION:

Individuals eligible to participate in this study must meet all of the following criteria:

1. Have completed the UX001-CL202, UX001-CL301, or UX001-CL203 studies
2. Willing and able to provide written, signed informed consent after the nature of the study has been explained, and before any research-related procedures are conducted
3. Willing to comply with all study procedures
4. Female participants of child-bearing potential or male participants with female partners of child-bearing potential who have not undergone a bilateral salpingo-oophorectomy and are sexually active must consent to use a highly effective method of contraception as determined by the site investigator (i.e., oral hormonal contraceptives, patch hormonal contraceptives, vaginal ring, intrauterine device, physical double-barrier methods, surgical hysterectomy, vasectomy, tubal ligation or true abstinence [when this is in line with the preferred and usual lifestyle of the subject], which means not having sex because the subject chooses not to), from the period following the signing of the informed consent through 30 days after last dose of study drug
5. Females of childbearing potential must have a negative pregnancy test at Screening and be willing to have additional pregnancy tests during the study. Females considered not of childbearing potential include those who have been in menopause for at least two years, have had tubal ligation at least one year prior to Screening, or who have had a total hysterectomy or bilateral salpingo-oophorectomy

Individuals who meet any of the following exclusion criteria will not be eligible to participate in the study:

1. Ingestion of N-acetyl-D-mannosamine (ManNAc) or related metabolites; intravenous immunoglobulin (IVIG); or anything that can be metabolized to produce SA in the body within 60 days prior to the Screening Visit
2. Has had any hypersensitivity to SA or its excipients that, in the judgment of the investigator, places the subject at increased risk for adverse effects
3. Pregnant or breastfeeding at Screening or planning to become pregnant (self or partner) at any time during the study
4. Use of any investigational product (except for Ace-ER/SA-ER as part of the parent study) or investigational medical device within 30 days prior to Screening, or anticipated requirement for any investigational agent prior to completion of all scheduled study assessments
5. Has a condition of such severity and acuity, in the opinion of the investigator, that it warrants immediate surgical intervention or other treatment or may not allow safe participation in the study
6. Has a concurrent disease, active suicidal ideation, or other condition that, in the view of the investigator, places the subject at high risk of poor treatment compliance or of not completing the study, or would interfere with study participation or would affect safety

INVESTIGATIONAL PRODUCT, DOSE, AND MODE OF ADMINISTRATION:

Each Ace-ER tablet contains 500 mg of SA in an extended release formulation for a total weight of 1200 mg/tablet. The drug will be administered by the oral route and will be divided into a TID regimen: 4 tablets taken in the morning, early evening, and before bedtime (qHS). The dose should be taken with food (i.e., within 30 minutes after a meal or snack).

REFERENCE THERAPY, DOSE, AND MODE OF ADMINISTRATION:

Not applicable

DURATION OF TREATMENT:

The total treatment duration will be 24 months. A Safety Follow-up visit will be conducted by phone 30 days (+5 days) after last dose of study drug.

CRITERIA FOR EVALUATION:

Safety:

Safety will be evaluated by the incidence frequency, and severity of AEs and SAEs, and clinically significant changes from baseline to scheduled time points in the following:

- Interval history
- Vital signs
- Physical examination results
- Clinical laboratory results
- C-SSRS (a measure of suicidal ideation and behavior)
- Concomitant medications

Drug Concentration Measurements:

Serum Free Sialic Acid: The change in free SA level in serum (trough) will reflect the absorption of SA during treatment.

Urine Sialic Acid - Free, Total and Bound: The urine SA level (corrected for creatinine) will reflect the absorption of SA and the incorporation into sialylated proteins and oligosaccharides during treatment.

Urine Testing for ManNAc: Urine will be tested for the presence of ManNAc to detect compliance with prohibited medication restrictions.

Efficacy:

Efficacy evaluations will be based on the parent study (UX001-CL202, UX001-CL301, or UX001-CL203) from which the subjects enroll. Subjects enrolling from UX001-CL202 will follow the same schedule of events as subjects who roll over from UX001-CL301. For UX001-CL202 subjects, assessments that cannot be safely performed by a subject due to disease progression should not be administered.

UX001-CL301 and UX001-CL202: For subjects enrolling from these studies, efficacy will be evaluated by changes in upper and lower extremity muscle strength and function, and self-reported physical functioning. Results from baseline assessments in this study will be compared with those of post-treatment assessments listed in the Schedule of Events (Table 2.1), with efficacy conclusions

based on change from baseline over the treatment period.

Primary Clinical Efficacy Variable :

Upper Extremity Composite Score: Muscle strength based on the maximum voluntary isometric contraction (MVIC) against a dynamometer will be measured bilaterally in the following upper extremity muscle groups: gross grip, shoulder abductors, elbow flexors, and elbow extensors. The UEC is derived from the sum of the average of the right and left total force values (measured in kg).

Secondary Clinical Efficacy Variables:

- GNEM Functional Activities Scale: Physical functioning will be assessed using a disease-specific measure. Scores on the mobility domain and the upper extremity domain of the GNEM-FAS will be analyzed separately as secondary variables.
- Lower Extremity Composite (LEC) Score: Muscle strength based on MVIC against a dynamometer will be measured bilaterally in the following lower extremity muscle groups: knee flexors, hip flexors, hip extensors, hip abductors and hip adductors. The LEC is derived from the sum of the average of the right and left total values (measured in kg).
- Number of Stands in the Sit-to-Stand Test: Lower extremity function will be 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 will be recorded.
- Number of Lifts in the 30-second Weighted Arm Lift Test: Upper extremity function will be 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 will be recorded.
- Total Force (kg) and Percent Predicted Force in the Knee Extensors: Bilateral total force will be reported. The percent predicted total force value will be determined based on reference equations adjusting for age, gender, height, and weight.
- Meters Walked in the Six-Minute Walk Test: The total distance walked (meters) in a six minute period will be measured as well as the percent predicted distance based on normative data for age and gender.

Tertiary Efficacy Variables:

- Upper Extremity Composite and Lower Extremity Composite Percent Predicted: The percent predicted total force values will be determined based on reference equations adjusting for age, gender, height, and weight. The percent predicted force will be calculated for each side and the bilateral percent predicted values will be averaged for each upper extremity muscle group. The mean of the four averages in percent predicted scores will be calculated to create a percent predicted UEC score, and analyzed relative to baseline to create a UEC mean change in percent predicted score. Similar methodology will be used to determine the percent predicted total force values for the LEC.
- Total Force (kg) and Percent Predicted in Each Individual Muscle Group: Bilateral total force and percent predicted total force for each individual muscle group included in the UEC and LEC will be reported.
- Total Score on the GNEM-FAS
- Self-Care Domain Score on the GNEM-FAS
- Score on the Individualized Neuromuscular Quality of Life Questionnaire: The scores on a 45-

item self-report questionnaire on the impact of key muscle disease symptoms on the ability to perform basic activities of daily living, functional independence, relationships and overall well-being will be recorded.

- Creatine Kinase Levels: CK levels in serum will be measured to assess the degree of reduction of CK levels observed as a surrogate for muscle injury.

UX001-CL203: Efficacy will be evaluated by changes in upper and lower extremity muscle strength, self-reported physical functioning, and health related quality of life outcome measures. Results from baseline assessments will be compared with those of post-treatment assessments listed in the Schedule of Events (Table 2.1), with efficacy conclusions based on change from baseline over the treatment period.

Clinical Efficacy Variables:

- GNEM-FAS – Expanded Version: Physical functioning will be assessed using a disease-specific, self-reported outcome measure. Scores on the mobility, self-care and upper extremity domains of the GNEM-FAS Expanded Version will be analyzed separately as secondary variables
- Upper Extremity Muscle Strength: Muscle strength measured as the maximum voluntary isometric contraction (MVIC) against a dynamometer will be measured bilaterally in the following upper extremity muscle groups: grip, key pinch, shoulder abductors and wrist extensors. A UEC, will be derived as the sum of the average of the right and left total force values (measured in kg) when force values are available for all muscle groups tested
- Lower Extremity Muscle Strength: Muscle strength based on the maximum voluntary isometric contraction (MVIC) against a dynamometer will be measured bilaterally for the knee extensors in subjects that can be positioned for testing.

Exploratory Variables:

- Short Form Health Survey-36 (SF-36): Quality of life will be assessed using the SF-36 with scores reported for the Physical Component Summary, Mental Component Summary and the eight subscales, including physical functioning, role-physical, bodily pain, general health, social functioning, role-emotional, vitality, and mental health
- Biomarkers: Serum will be obtained at all study visits to evaluate CK, serum aceneuramic acid, and potential biomarkers of sialylation and other markers of muscle injury and remodeling

STATISTICAL METHODS:

Sample Size:

Approximately 165 adult subjects with GNEM are expected to roll-over from UX001-CL202 (N=55), UX001-CL301 (N=80), and UX001-CL203 (N=30) studies to participate in this extension study.

Efficacy Analyses:

Separate analyses will be performed for subjects enrolling from each parent study.

The full analysis set will include all subjects with a baseline measurement and at least one post-baseline measurement. This set will be used for the analyses of all efficacy endpoints.

Baseline values for each endpoint will be defined as the last scheduled data collection visit before first dose according to the Schedule of Events (Table 2.1).

Efficacy analyses will use generalized estimating equation (GEE) to evaluate trends over time with respect the changes from baseline for the primary variables, and all secondary and tertiary efficacy variables. Baseline will be included as a covariate in the model. This method will be the primary analysis method for all repeated measures endpoints.

The statistical analyses will be reported using summary tables, figures, and data listings. Statistical tests will be 2-sided at the alpha=0.05 significance level. Continuous variables will be summarized with means, standard deviations, medians, minimums, and maximums. Categorical variables will be summarized by counts and by percentages of subjects in corresponding categories.

Safety Analyses:

Safety will be evaluated for the overall study population as well as for subjects from the UX001-CL202, UX001-CL301, and UX001-CL203 studies. The safety analysis set consists of all subjects who receive at least one dose of study drug. Safety will be evaluated by the incidence, frequency, and severity of AEs and SAEs, and clinically significant changes from study baseline to scheduled time points in: interval history, vital signs, physical examination findings, clinical laboratory evaluations, C-SSRS, and concomitant medications

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).
The incidence and frequency of AEs will be summarized by System Organ Class (SOC), Preferred Term (PT), severity, and relationship to treatment. The numbers (frequency) and incidence rates of AEs and SAEs will be summarized by treatment group. A by-subject listing will be provided for those subjects who experience a serious adverse event (SAE), including death, or experience an adverse event (AE) associated with early withdrawal from the study or study drug treatment.

Clinical laboratory data will be summarized by the type of laboratory test. The frequency and percentage of subjects who experience abnormal clinical laboratory results (i.e. outside of reference ranges) and/or clinically significant abnormalities will be presented for each clinical laboratory measurement.

Table 2.1: Schedule of Events

Assessments and Events*	Screening/ Baseline[a]	Treatment Period						
		Month 2 (Week 8) Visit (± 5 days)‡	Month 4 (Week 16) Visit (± 5 days) ‡	Month 6 (Week 24) Visit (± 5 days)	Month 12 Visit (Week 48) (± 2weeks)	Month 18 Visit (Week 72) (± 2weeks)	Month 24 (Week 96) OR Early Termination Visit (± 2weeks) [l]	Safety Follow Up (+ 5 days) [m]
Safety Assessments (All Subjects)								
Informed consent	X							
Medical History	X							
Interval history [b]	X	X	X	X	X	X	X	
Physical examination [c]	X	X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	X	
Hematology, chemistry panel, urinalysis	X	X	X	X	X	X	X	
Pregnancy test	X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X
Suicidal ideation and behavior (C-SSRS) [d]	X	X	X	X	X	X	X	
Adverse events	X	X	X	X	X	X	X	X
Pharmacodynamic Assessments (All Subjects)								
Biomarkers: CK, Free serum SA, and Biomarkers of Sialyation and Other Biomarkers [e]	X	X	X	X	X	X	X	
Free, total and bound urine SA levels [f]	X	X	X	X	X	X	X	
Urine test for ManNAc [g]	X	X	X	X	X	X	X	

Assessments and Events*	Screening/ Baseline[a]	Treatment Period						
		Month 2 (Week 8) Visit (± 5 days)‡	Month 4 (Week 16) Visit (± 5 days)‡	Month 6 (Week 24) Visit (± 5 days)	Month 12 Visit (Week 48) (± 2weeks)	Month 18 Visit (Week 72) (± 2weeks)	Month 24 (Week 96) OR Early Termination Visit (± 2weeks)[l]	Safety Follow Up (+ 5 days)[m]
Treatment Dispensing and Compliance (All Subjects)								
Treatment dispensed[h]	X	X	X	X	X	X		
Treatment compliance		X	X	X	X	X	X	
Efficacy Assessments (UX001-CL202 and UX001-CL301 Subjects)[i]								
Dynamometry	X	X	X	X	X	X	X	
6-minute walk test (6MWT)	X	X	X	X	X	X	X	
Sit-to-stand test	X	X	X	X	X	X	X	
Weighted arm lift test	X	X	X	X	X	X	X	
GNE Myopathy Functional Activities Scale (GNEM-FAS)	X	X	X	X	X	X	X	
Individualized Neuromuscular Quality of Life Questionnaire (INQoL)	X	X	X	X	X	X	X	
Efficacy Assessments (UX001-CL203 Subjects)								
Dynamometry[j]	X			X	X	X	X	
GNEM-FAS[k]	X			X	X	X	X	
Short Form Health Survey-36 (SF-36)	X			X	X	X	X	

* Refer to study-related materials for recommended timing and order of assessments to be administered at each study visit.

ǂ Subjects who roll-over from the UX001-CL203 study will not have a Month 2 or Month 4 visit. Assessments at these visits will only be performed for subjects who roll-over from the UX001-CL202 and UX001-CL301 studies. UX001-CL202 subjects will complete the same efficacy assessments as the subjects who rollover from UX001-CL301.

a. Potential subjects can be screened up to 5 days after the last dose on the parent study. Baseline Visit should be not be more than 5 days after Screening visit. Subjects can have a concurrent Screening and Baseline visits. Study drug will be dispensed only after all study procedures at the Baseline Visit have been performed. For subjects who discontinue prior to completing the study, every reasonable effort should be made to perform the Early Termination (ET) procedures within four weeks of discontinuation.

b. Interval history will include any signs, symptoms, or events (i.e. falls) experienced by the subject since the prior study visit that are not related to study procedure(s) performed at prior study visits or study drug. Interval history may include exacerbation or improvement in existing medical conditions (including the clinical manifestations of GNEM) that might interfere with study participation, safety, and/or positively or negatively impact performance of functional assessments.

c. The physical examinations at Baseline/Screening, including a neurological examination; all others will be brief physical examinations. If a patient is unable to stand or has significant postural issues that interfere with collection of a standing height, self-reported adult height should be captured.

d. Baseline C-SSRS administered at Baseline/Screening visit (may be same as last visit in parent study). Since Last Visit C-SSRS administered at all subsequent visits.

e. Serum will be obtained at all study visits to evaluate creatine kinase (CK), serum SA and potential biomarkers of sialylation, and other markers of muscle injury and remodeling.

f. Blood samples, preferably pre dose, and first-morning void urine will be collected to assess trough SA levels; record volume of urine collected.

g. An aliquot from first morning void urine will be used for assessment of ManNAc; record volume of urine collected.

h. Subjects should be instructed to return unused study drug and packaging to every visit. Note that all subjects being treated with 12 g/day Ace-ER in UX001-CL202 will be transitioned to 6 g/day Ace-ER dose in this protocol.

i. For UX001-CL202 subjects, assessments that cannot be safely performed by a subject due to disease progression should not be administered.

j. For subjects enrolling from UX001-CL203, lower extremity muscle strength for knee extensors muscle group only.

k. For subjects enrolling from UX001-CL203, the GNEM-FAS Expanded version will be used.

l. The Early Termination Visit occurs if a subject discontinues prior to completing the study or no longer wants to participate in the study. Every reasonable effort should be made to have subjects return to the clinic within 4 weeks of discontinuation and perform the Early Termination procedures; however, subjects who are unable to return to the clinic will be given the option of having an Early Termination Visit telephone call within 4 weeks of discontinuation from study, where appropriate information will be collected by the clinical site.

m. Safety Follow-up visit to be conducted by phone 30 days (+5 days) after last dose of study drug.

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4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviations

6MWT	Six Minute Walk Test
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATS	American Thoracic Society
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
cGMP	Current Good Manufacturing Practices
CK	creatine kinase
CRF	Case Report Form
C-SSRS	Columbia-Suicide Severity Rating Scale
DMRV	distal myopathy with rimmed vacuoles
EC	Ethics Committee
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEE	generalized estimating equation
GI	gastrointestinal
GlcNAc	N acetyl-glucosamine
GNE/MNK	glucosamine (UDP-N-acetyl)-2-epimerase/N-acetylmannosamine kinase
GNEM	GNE Myopathy
GNEM-FAS	GNE Myopathy Functional Activities Scale
hERG	human ether-à-go-go-related gene
HIBM	hereditary inclusion body myopathy
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IND	Investigational New Drug (application)
INQoL	Individualized Neuromuscular Quality of Life Questionnaire
IRB	Institutional Review Board
IVIG	intravenous immune globulin

LDH	lactate dehydrogenase
LEC	Lower extremity composite
ManNAc	N-acetyl-D-mannosamine
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MVIC	maximum voluntary isometric contraction
NANA	N-acetylneuraminic acid
NF	National Formulary
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOAEL	no observed adverse effect level
PD	pharmacodynamic
PK	pharmacokinetic(s)
PT	Preferred Term
qHS	at the time of sleep (i.e., at bedtime)
QSM	quadriceps sparing myopathy
RBC	red blood cell
RSI	Reference Safety Information
SA	sialic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SUSAR	suspected unexpected serious adverse reactions
TID	three times per day
UEC	Upper extremity composite
ULN	upper limit of normal
US	United States
USP	United States Pharmacopeia
WBC	White blood cell

Definition of Terms

Investigational Product is defined as, "A pharmaceutical form of an active ingredient being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use" (from International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use [ICH] Harmonised Tripartite Guideline E6: Guideline for Good Clinical Practice).

The terms "Investigational Product" and "study drug" may be used interchangeably in the protocol.

5 INTRODUCTION

The product under investigation is sialic acid (SA) administered in extended release (Ace-ER) tablets. Ace-ER is intended for use as a substrate replacement therapy for the treatment of GNE Myopathy (GNEM), also known as Hereditary Inclusion Body Myopathy (HIBM), Quadriceps Sparing Myopathy (QSM), Inclusion Body Myopathy type 2, Distal Myopathy with Rimmed Vacuoles (DMRV), and Nonaka myopathy (Huizing et al. 2009); (Jay et al. 2009); (Malicdan et al. 2008). Currently there are no approved treatments for GNEM.

SA is an essential, naturally occurring amino sugar found in humans and most organisms. Defects in the SA biosynthetic pathway cause GNEM, a severe progressive myopathy. By replacing SA substrate, sialylation should be restored on key target glycoproteins and glycolipids, leading to restoration of biochemical function, improved muscle physiology and improved clinical function. The scientific rationale is primarily based on the nature of the underlying genetic defect supported by proof of concept work in a knockout mouse that models the muscle disease and pathology of HIBM (Malicdan et al. 2009). The safety of SA has been studied in chronic treatment studies in HIBM mice and toxicology studies in multiple species of normal animals. These data demonstrated reasonable safety for SA and established a no adverse effect level (NOAEL) of 2,000 mg/kg in rats and dogs, enabling clinical studies in GNEM patients.

Ultragenyx has developed Ace-ER tablets since successful use of SA replacement therapy in humans is believed to depend upon optimized exposure to the compound. SA has a half-life of less than 1 hour in the circulation (Malicdan et al. 2009). Ace-ER was developed to improve the stability of exposure to SA and allow more appropriate dosing and efficient substrate replacement. The Ace-ER formulation was evaluated in an initial Phase 1 study to establish the safety and pharmacokinetic (PK) profile of a single dose and 7 days of repeat dosing in SA-deficient GNEM patients. The study drug was well tolerated at all dose levels. There were no serious adverse events (SAEs), and all adverse events (AEs) were mild to moderate with no dose relationship or pattern.

A Phase 2 randomized, placebo-controlled study evaluated chronic dosing of Ace-ER at two dose levels to establish the pharmacodynamic (PD) effects of SA on sialylation, identify the appropriate dose level, and provide insight into clinical efficacy and safety. Data from the Phase 2 study demonstrated efficacy and acceptable safety profile at the 6 g/day Ace-ER dose level. In addition, a Phase 3 study (UX001-CL301) in subjects able to walk at least 200 m in the 6-minute walk test (6MWT) and a Phase 2 open-label study (UX001-CL203) designed primarily to evaluate the safety of 6 g/day Ace-ER tablets in GNEM patients who have severe ambulatory impairment are currently ongoing. Although safety is the primary objective, efficacy in this study will also be assessed as a secondary objective to ensure that the full spectrum of patients with GNEM is evaluated across the development program.

Ultragenyx is also sponsoring a GNEM Disease Monitoring Program (GNEM-DMP) which includes a disease registry (a longitudinal patient reported disease outcome survey) and a

natural history study (a physician-reported protocol-driven formal study). The GNEM-DMP is being conducted in parallel with the SA clinical development program to collect data on disease characteristics and progression.

This Phase 3b extension study is designed to confirm the long-term safety and efficacy of 6 g/day Ace-ER tablets in GNEM patients.

5.1 Overview of GNE Myopathy

GNE Myopathy (GNEM) is a rare and severely debilitating disease of adult onset myopathy and progressive muscle weakness. The disease has been known by other names such as HIBM and Nonaka disease but the new name of GNEM is preferred because it reflects the underlying genetic cause of the disease (Huizing et al. 2014). GNEM is an autosomal recessive disorder caused by a mutation in the GNE gene, which encodes an enzyme critical to the biosynthesis of SA. SA is an endogenous monosaccharide that is thought to play a role in stabilization of muscle cell membranes through sialylation of extracellular proteins. Magnetic resonance imaging (MRI) radiography and muscle biopsy analysis demonstrate irreversible replacement of muscle tissue with fat and fibrosis, suggesting that the hyposialylated proteins in GNEM are dysfunctional and lead to cell death (Huizing et al. 2009).

Patients with GNEM typically present with distal muscle weakness, most commonly but not exclusively presenting as foot drop. As the disease progresses, the atrophy spreads to affect not only the lower extremities but the upper extremities as well, leading to loss of ambulation and as reliance on others for care (to feed oneself, for example). Assistive devices such as ankle-foot orthoses (AFOs) with a rigid base are often used to allow the patients to walk, albeit with a slow, unsteady gait, through leveraging the quadriceps muscle, which is typically spared in GNEM. There are no approved medical therapies to treat the disease and patients typically become wheelchair bound after 10-20 years from initial diagnosis (Nonaka et al. 2005).

The identification of the genetic deficiency of SA biosynthesis in GNEM suggested that SA replacement provided exogenously to GNEM patients may be able to restore SA levels in the cell and thereby restore sialylation of proteins and lipids in the muscle.

5.2 Brief Overview of Ace-ER Development

Ace-ER tablets are in development as a treatment for GNEM. The scientific rationale for SA substrate replacement therapy is based on the identification of the genetic deficiency of SA biosynthesis in GNEM which suggested that SA replacement provided exogenously to GNEM patients may be able to restore SA levels in the cell and thereby restore sialylation of proteins and lipids in the muscle. Studies in animal models showed that *GNE* missense mutations caused decreased sialylation and that the phenotype resembles human disease (Malicdan et al. 2009). Specifically, murine GNEM knockout/knockin models have low SA levels, decreased muscle strength and function, and histopathology resembling the human phenotype (Malicdan et al. 2009). In the animal models, exogenously administered SA was

absorbed and taken up into cells, leading to increased sialyation in muscle tissue (Malicdan et al. 2009, Bardor et al. 2005, Oetke et al. 2001). Prophylactic or symptomatic substrate replacement therapy with SA or its derivatives substantially improved muscle strength and histology with only relatively small increases in SA levels (Malicdan et al. 2009), (Yonekawa et al. 2014). Nonclinical studies have been conducted in HIBM mice and multiple species of normal animals. Two clinical studies and an extension study have also been conducted to characterize the PK, tolerability, safety, and efficacy of SA replacement in GNEM patients; in addition, UX001-CL301 and UX001-CL203 are currently ongoing.

A brief overview of existing information on Ace-ER is provided below; a comprehensive review of available data is contained in the investigator's brochure (IB) provided by Ultragenyx Pharmaceutical Inc. (Ultragenyx), which should be reviewed prior to initiating the study.

5.2.1 Brief Description of Ace-ER

SA (also known as N-acetylneuraminic acid [NANA]) is an essential, naturally occurring amino sugar found in man and most organisms. An extended-release form of SA was developed to improve the stability of exposure to SA in vivo and allow more appropriate dosing and efficient substrate replacement. The choice of an extended release formulation is based on the fact that SA has a short half-life in the circulation and its rapid clearance makes it difficult to use as a therapeutic replacement substrate in which a steady and constant supply of SA is needed.

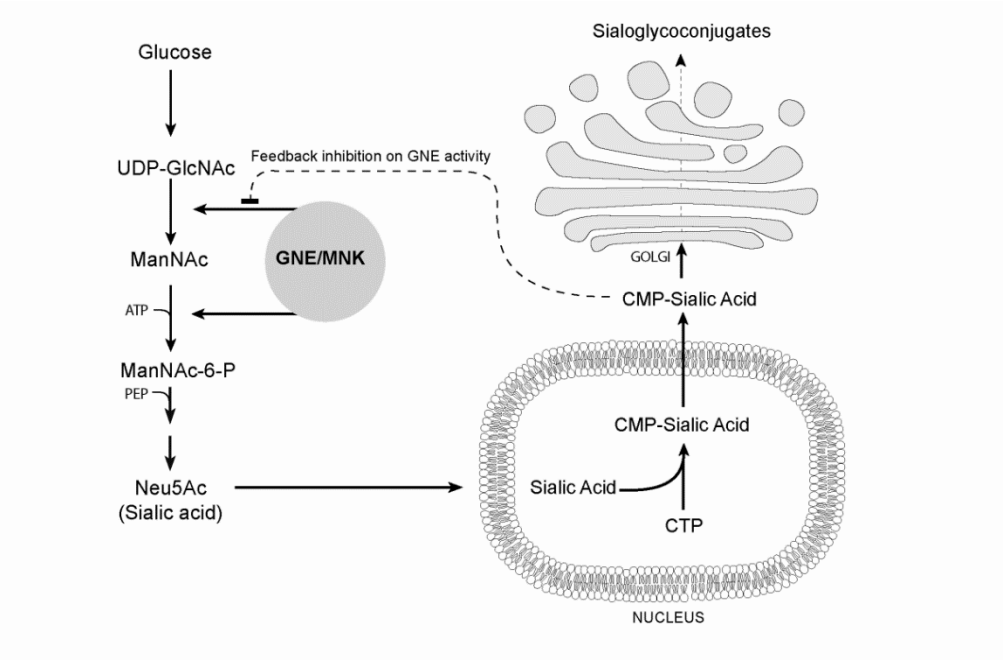
The active SA pharmaceutical ingredient is produced synthetically in an enzyme-catalyzed two step reaction where N acetyl-glucosamine (GlcNAc) is converted into SA.
No mammalian sourced products are used in the production of SA. The product is purified and crystallized yielding high purity SA which is formulated into Ace-ER tablets using United States Pharmacopoeia (USP)/National Formulary (NF) excipients commonly used for this purpose.

Ace-ER 500 mg tablets are white to off-white, film-coated, extended-release, oval tablets, which may be debossed with the code U-1 and are designed for oral administration.

5.2.1.1 Mechanism of Action in GNE Myopathy

The glucosamine (UDP-N-acetyl)-2-epimerase/N-acetylmannosamine kinase (GNE/MNK) enzyme is the rate-controlled and regulated first step in the biosynthesis of SA required for the glycosylation of proteins and lipids (Figure 5.2.1.1.1). Genetic defects in the SA biosynthetic pathway cause GNEM, a severe progressive myopathy. By replacing SA substrate via Ace-ER, sialylation should be restored on key target glycoproteins and glycolipids, and lead to restoration of biochemical function, improved muscle physiology and improved clinical function.

Figure 5.2.1.1.1: The Biosynthetic Pathway of Sialic Acid in its Subcellular Locations



5.2.2 Nonclinical Studies

Published studies in the HIBM mouse model have shown that SA replacement can reduce muscle weakness and atrophy, improve muscle pathology and function, and restore sialylation in muscle (Malicdan et al. 2009; Yonekawa et al. 2014). The rational basis for the use of SA as a therapy in GNEM is primarily dependent on these results. Key safety pharmacology, PK, and toxicology studies to support the use of SA in treating GNEM are summarized below; additional details may be found in the IB.

Safety pharmacology: Ultragenyx conducted the core battery of safety pharmacology studies of Ace-ER that are recommended by ICH guidelines. These studies consisted of *in vitro* human ether-à-go-go-related gene (hERG) channel inhibition, neurobehavior in rats, and respiratory and cardiovascular evaluations in dogs after oral administration of SA. SA did not show any potential for QT prolongation in the hERG assay at concentrations as high as 6×10^{-3} mol/L (1855 µg/mL). No adverse effects on neurobehavior in rats or on respiratory and cardiovascular function in dogs were observed at oral SA doses as high as 2000 mg/kg/day.

Pharmacokinetics: PK of aceneuramic acid has been demonstrated through a series of experiments, including pharmacology studies in HIBM mice, supportive PK studies in rats with SA or KI-111, a single dose non-GLP PK study with aceneuramic acid, a pilot single dose non-GLP PK study of aceneuramic acid in dogs, and three multiple dose non-GLP PK studies of aceneuramic acid in dogs. Additionally, toxicokinetics were evaluated as part of a 26-week GLP toxicology study in and a 39-week GLP toxicology study in dogs. Finally, a

series of in vitro experiments was conducted for aceneuramic acid to investigate the potential for cytochrome P450 inhibition, cytochrome P450 induction, and to determine if aceneuramic acid is an inhibitor or a substrate of human efflux and uptake transporters. These PK studies demonstrated that SA was quickly excreted primarily through the urine. High tissue distribution was observed in the kidney and bladder, and distribution of radioactivity to skeletal muscle was confirmed. Radioactivity levels in most tissues, including serum, reached their highest concentration within 0.5 hours post dose, then fell quickly up to 3 hours post-dose. Radioactivity extraction by methanol suggested existing forms in the serum at 3 hours post-dose are not unchanged. PK in the HIBM mouse model confirmed that the serum concentration of SA peaked quickly and was rapidly excreted in the urine. Additional PK studies conducted with aceneuramic acid (extended release compared with co-administration of extended release and immediate release formulations, or with a bilayer tablet) administered orally to dogs showed that the prolonged release tablet maintains an extended duration of plasma levels of SA in comparison to free SA. Furthermore, the in vitro cytochrome P450 and transporter studies indicated that there is no potential for interference by aceneuramic acid on the metabolism of other drugs.

Chronic toxicology studies in rats and dogs: In an oral 26-week rat study, there were no Ace-ER treatment-related effects on clinical condition, body weight, food consumption, ophthalmology, clinical pathology (hematology, blood chemistry, and urinalysis) or in pathologic evaluations (gross, organ weight, and histopathology). The NOAEL in the 26-week toxicity study in rats was 2000 mg/kg/day, which reflects a safety margin of approximately 3.2-fold by dose (13-fold by C_{max}; 2.9-fold by AUC) over the proposed efficacious dose of 6g/day. A 39-week oral toxicity study in dogs did not show any adverse effects on clinical condition, body weight, food consumption ophthalmology, electrocardiography, and clinical pathology (hematology, blood chemistry, and urinalysis). The NOAEL in the 39-week toxicity study in dogs was 2000 mg/kg/day, which reflects a safety margin of approximately 11–fold by dose (136-fold by C_{max}; 28-fold by AUC) over the proposed efficacious dose of 6 g/day.

Reproductive and developmental toxicology studies in rats and rabbits: Developmental and reproductive toxicity studies at oral doses as high as 2000 mg/kg/day have not shown any adverse effects on fertility of male or female rats, treatment-related effects on dams or embryo-fetal development parameters in rats and rabbits, or treatment-related effects on pre-and post-natal development in rats.

Genotoxicity: A standard battery of GLP genotoxicity tests was performed with aceneuramic acid and there was no evidence of any genotoxic, clastogenic or mutagenic effects. In these studies, aceneuramic acid was tested at concentrations of 1.58 to 5000 µg/plate in the *in vitro* bacterial mutation assay and 0.625 to 310 µg/mL in the *in vitro* clastogenicity assay in human peripheral blood lymphocytes. For the mouse micronucleus assay, aceneuramic acid was given as 2 doses, 24 hours apart, by oral gavage (500, 1000, or 2000 mg/kg/day).

5.2.3 Previous Clinical Studies

Key results from studies to support the use of SA in treating GNEM are summarized below; additional details may be found in the IB.

Phase 1 Pharmacokinetic and Safety Study (UX001-CL101):

The exposure of aceneuramic acid in adult GNEM patients was characterized in study UX001 CL101 following single (fasted and fed) and repeat doses of Ace-ER up to 6000 mg/day for 7 days. The PK parameters derived from traditional non-compartmental analysis are presented in UX001-CL101 following single dose administration (fasted and fed states) and repeat dosing (steady state). Following single oral administration of Ace-ER (fasted or fed), the maximum baseline-adjusted SA concentration in serum was achieved in approximately 3 to 10 hours. The Cmax increased in a less than dose proportional fashion across the dose range studied, showing a 2.7-fold increase between the 650 mg and 6000 mg dose groups.

Observed results from single-dose administration demonstrate that adequate absorption of the drug, with or without food, occurs at all dose levels. The impact of food on exposure is complex with some dose levels showing higher AUC with fasted conditions (650 mg and 4875 mg dose), similar AUC under both fasted and fed conditions (2925 mg dose), and higher AUC with food (1950 and 6000 mg dose). For the 6000 mg dose, the AUC was significantly greater (~46%) when administered in the fed state at 3.934 mcg*hr/ml compared with 2.592 mcg*hr/ml fasted. Given that the 6000 mg dose was administered using the 500 mg tablet, the differences observed may be due to a subtle effect of the larger tablet size on the absorption rate and/or duration, even though in vitro dissolution data is comparable for the 325 mg and 500 mg tablets. The larger tablet may have a longer time of release in vivo. This difference coupled with a food effect prolonging aceneuramic acid exit from the stomach may enhance the overall absorption of aceneuramic acid (acidity should improve aceneuramic acid absorption by neutralizing its charge).

Phase 2 Pharmacokinetic, Pharmacodynamic and Safety Study (UX001-CL201):

The Phase 2, randomized, double-blind, placebo-controlled study UX001-CL201 evaluated the safety and efficacy of Ace-ER 3 g/day or 6 g/day, versus placebo in ambulatory subjects with GNEM (n=47). Because the study evaluated both efficacy and safety in a blinded manner for the full 48 weeks (first 24 weeks placebo controlled and last 24 weeks all subjects on either 6 g/day or 3 g/day), it allows for evaluation of efficacy during one year.
The inclusion criteria for UX001-CL201 also allowed for the enrollment of subjects with a broad spectrum of physical disability, with at least 60% of enrolled subjects having residual lower extremity strength and function sufficient to walk ≥ 200 m in the 6MWT at screening. Enrolling subjects across a spectrum of disease severity allowed the study to fully evaluate the safety and efficacy profile.

Ace-ER at a dose of 6 g/day stabilized upper extremity muscle strength compared with declines for placebo at 24 weeks and 3g/day at 48 weeks. The result is consistent as each

muscle group included in the composite evaluation favored 6 g/day over 3 g/day or placebo in all analyses. Additionally, a larger treatment difference was observed in subjects with more viable muscle tissue (able to walk at least 200 m in the 6MWT at Baseline) who had a larger treatment difference over 48 weeks (+4.69 kg; p=0.0005).

Overall, a lower extremity composite (LEC) results were directionally in favor of the 6 g/day group over 48 weeks, although not statistically significant. Baseline muscle strength is far more impaired in the lower extremities, which may impact the ability to have and/or see a treatment effect. An analysis of changes in LEC scores over 48 weeks for the 6/6 g/day Ace-ER group versus the 0/3 g/day Ace-ER group was conducted to evaluate LE outcomes when comparing the highest and lowest exposure groups. The difference between the groups was +3.37 kg; p=0.16. In comparing the highest and lowest dose exposure groups over 48 weeks, the high dose group that received 6 g/day throughout the 48 weeks retained substantially more LE strength than the subjects who received placebo for 24 weeks followed by 3 g/day treatment.

Phase 2 Efficacy and Safety Extension Study (UX001-CL202):

In addition to the study data from UX001-CL201, the UX001-CL202 study allowed for the continuation of open-label treatment with 6 g/day of Ace-ER in the original 46 subjects who crossed over to UX001-CL202. In addition, 13 subjects who were naïve to Ace-ER and who could walk ≥ 200 m in the 6MWT were enrolled.

In the UX001-CL202 extension study, after approximately 2.5 years of treatment over the course of two studies in subjects with a progressive, debilitating disease, muscle strength remained stable in 7 of 9 of the individual muscle groups comprising the upper extremity composite (UEC) and the LEC muscle strength scores in the combined 0/6 and 6/6 group. Grip strength and hip abductors decreased modestly from original study baseline, resulting in decreases in overall UEC and LEC muscle strength scores.

For both the upper and lower extremities, subjects treated with 6 g/day at the beginning of the 201 study had the greatest strength at the end of approximately 2.5 years compared to patients who started 6g at Week 24 or received 3 g/day at any time during the first year.

5.2.4 Summary of Overall Risks and Potential Benefits

GNEM is a rare and severely debilitating disease of adult onset myopathy and progressive muscle weakness with no currently approved therapy and significant unmet medical need. Strong pre-clinical evidence demonstrated that direct substrate replacement therapy may be a promising therapeutic approach for patients with GNEM. Aceneuramic acid is chemically identical to the endogenous monosaccharide sialic acid and its extended release formulation leads to stable improvement of SA levels.

Aceneuramic acid at a dose of 6 g/day has demonstrated positive pharmacodynamic effects such as increasing tissue and serum SA levels as well as lowering of serum creatine kinase

(CK) levels that support the clinical efficacy observed in a randomized, double-blind, placebo-controlled study. The clinical efficacy data at 6 g/day demonstrates muscle strength stabilization and preservation of functional independence relative to placebo or lower dose treatment. Safety information collected over approximately 2.5 years demonstrates that aceneuramic acid has a favorable safety profile.

Each clinical study assessed AEs and SAEs at every scheduled study visit from the time of informed consent. As expected with a substrate replacement therapy, Ace-ER has been well tolerated in clinical studies to date. Levels of free SA in serum during 6 g/day administration were only 2 fold greater than in healthy volunteers. There have been no treatment-related serious adverse events and only one withdrawal due to an adverse event over the 2.5 years of observation. Acceptable tolerability has also been demonstrated by a high treatment compliance rate as well by the fact that all subjects who completed the pivotal study elected to participate in the extension study. The incidence of adverse events of gastrointestinal (GI) disturbance including flatulence, dyspepsia, and diarrhoea were greater in the treatment groups than placebo during the first 24 weeks of the pivotal study. Exposure adjusted rates of these GI events were similar when comparing 6 g/day to placebo. Mildly elevated transaminases occurred but were considered most likely related to the underlying skeletal muscle disease rather than to liver injury.

Ace-ER treatment at 6 g/day clearly has a positive benefit-risk profile that supports the proposed indication of treatment of adult patients with GNEM, and has the potential to impact an unmet medical need for GNEM patients.

5.3 Study Rationale

GNEM (or HIBM), is a severe, progressive myopathy caused by a defect in the biosynthetic pathway for SA. Substrate replacement is a potential therapeutic strategy based on the success of replacing missing SA and reducing muscle disease in a relevant mouse model of the human disease. Successful use of SA replacement therapy in humans is believed to depend upon providing steady, long-term exposure to the compound in an extended-release form (such as Ace-ER), given SA's short half-life. A Phase 2, placebo-controlled study evaluating Ace-ER at 2 doses for 48 weeks (UX001-CL201) found that the higher dose of 6 g/day Ace-ER stabilized UEC score compared with placebo or the lower 3 g/day dose; this finding was supported by measurements of functional outcome on the GNE Myopathy Functional Activities Scale (GNEM-FAS). This Phase 3b extension study will assess the long-term safety of Ace-ER in subjects who completed the UX001-CL202, UX001-CL301, or UX001-CL203 studies; in addition, efficacy of 6 g/day Ace-ER will be further evaluated in GNEM patients, including those able to walk ≥200 m in the 6MWT (roll over subjects from UX001-CL301 and naïve subjects from UX001-CL202) and GNEM patients with severe ambulatory impairment (roll over subjects from UX001-CL203).

6 STUDY OBJECTIVES

- To evaluate the long-term safety and efficacy of Ace-ER treatment of GNE Myopathy subjects

6.1 Study Endpoints

Overall Safety Endpoint (Primary Endpoint): Evaluate the long-term safety of 6 g/day Ace-ER treatment in subjects with GNE Myopathy

Overall Efficacy Endpoint: Evaluate the long-term effect of 6 g/day of Ace-ER treatment in subjects with GNEM. Efficacy will be evaluated as follows:

For Subjects Enrolling from UX001-CL202 and UX001-CL301:

- Muscle strength as measured by dynamometry
- Mobility, strength, and function using a series of physical performance measures
- Functional disability using an patient- and clinician-reported questionnaire

For Subjects Enrolling from UX001-CL203:

- Change in GNEM-FAS Expanded Version total score and mobility, upper extremity and self-care domain scores
- Change in upper extremity strength in grip, key pinch, shoulder abductors and wrist extensors and in lower extremity muscle strength in the knee extensors as measured by dynamometry
- Evaluate the effect on 6g/day Ace-ER on health-related quality of life, patient reported outcomes (PRO), and biomarkers of sialyation

7 INVESTIGATIONAL PLAN

7.1 Overall Study Design and Plan

This open-label extension study of will assess the long-term safety and efficacy of Ace-ER treatment over a period of 24 months. Approximately 165 subjects from the UX001-CL202, UX001-CL301, and UX001-CL203 studies will be eligible to enroll in the study.

Subjects will take 4 tablets (500 mg Ace-ER each for 2 g per dose) orally 3 times per day (TID). The dose should be taken with food (i.e. within 30 minutes after a meal or snack). Subjects being treated with 12 g/day Ace-ER in UX001-CL202 will be transitioned to 6 g/day Ace-ER dose in this protocol. Treatment will be administered for a total of 24 months. Study visits will occur every 8 weeks for 24 weeks and then every 6 months for subjects enrolling from UX001-CL202 or UX001-CL301. For subjects enrolling from UX001-CL203 studies, study visits will occur every 6 months (Table 2.1).

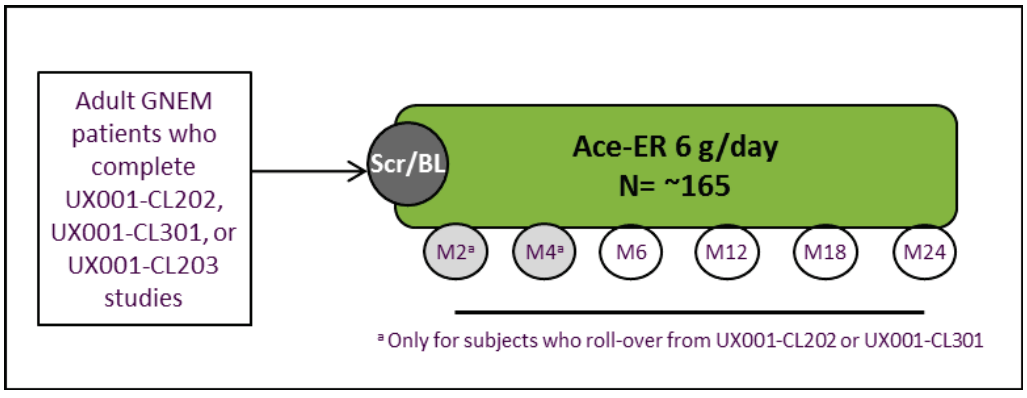
Safety will be evaluated by review of the incidence and frequency of AEs and SAEs and clinically significant changes in interval history, physical examination results, vital signs, clinical laboratory test results, the Columbia Suicide Severity Rating Scale (C-SSRS), and concomitant medications.

Blood samples will be collected to evaluate biomarkers (for example sialylation of serum proteins before and after treatment) to determine their utility in predicting clinical outcomes.

Efficacy will be evaluated based on assessments used in the parent study from which subjects roll over (subjects enrolling from UX001-CL202 will follow the same schedule of events as subjects who roll over from UX001-CL301), and include dynamometry as a measure of muscle strength and patient- and clinician-reported outcome measures as indicators of physical functioning and quality of life. For UX001-CL202 subjects, assessments that cannot be safely performed by a subject due to disease progression should not be administered.

Figure 7.1.1 provides a schematic of the study design.

Figure 7.1.1: Study Schema



7.2 Discussion of Study Design

This Phase 3b study is designed to be a long-term safety and efficacy study of 6 g/day Ace-ER in GNEM patients. The study will assess long-term effects of Ace-ER on clinical measures of muscle strength, mobility, function, ability and health-related quality of life. The primary endpoint of the study is safety.

The treatment duration of up to 24 months is intended to evaluate the long-term safety and efficacy of Ace-ER. The study is limited to GNEM patients who have completed UX001-CL202 (open label, safety study in GNEM patients), UX001-CL301 (randomized, double-blind, placebo-controlled, Phase 3 study), or UX001-CL203 (open label, safety study in GNEM patients with severe ambulatory impairment).

The study will assess the safety of the study drug by the incidence and frequency of adverse events and serious adverse events. Any significant changes from baseline to scheduled time points in concomitant medications, physical examination results, vital signs, clinical laboratory test results, interval history, and C-SSRS will also be part of the safety evaluation.

7.3 Selection of Study Population

This study will be conducted in adults who have previously documented mutations in the gene for the GNE/MNK enzyme leading to a diagnosis of GNEM (variously termed HIBM, DMRV, or Nonaka disease). These patients have an impaired ability to synthesize endogenous SA, which leads to muscle weakness and atrophy. Consequently, this is the relevant population for testing SA replacement therapy, and for determining if SA replacement leads to improved protein and lipid sialylation and stabilized or improved muscle structure and performance.

Individuals who have ingested N-acetyl-D-mannosamine (ManNAc) or similar other SA-producing compounds during the 60 days prior to the Screening Visit will be excluded as it could confound interpretation of the results. See Section 7.3.1 and 7.3.2 for complete Inclusion and Exclusion criteria.

7.3.1 Inclusion Criteria

Individuals eligible to participate in this study must meet all of the following criteria:

1) Have completed UX001-CL202, UX001-CL301, or UX001-CL203 studies
2) Willing and able to provide written, signed informed consent after the nature of the study has been explained, and before any research-related procedures are conducted

3) Willing to comply with all study procedures
4) Female participants of child-bearing potential or male participants with partners of child-bearing potential who have not undergone a bilateral salpingo-oophorectomy and are sexually active must consent to use a highly effective method of contraception as determined by the site investigator (i.e. oral hormonal contraceptives, patch hormonal contraceptives, vaginal ring, intrauterine device, physical double-barrier methods, surgical hysterectomy, vasectomy, tubal ligation or true abstinence [when this is in line with the preferred and usual lifestyle of the subject], which means not having sex because the subject chooses not to), from the period following the signing of the informed consent through 30 days after last dose of study drug
5) Females of childbearing potential must have a negative pregnancy test at Screening and be willing to have additional pregnancy tests during the study. Females considered not of childbearing potential include those who have been in menopause for at least two years, have had tubal ligation at least one year prior to Screening, or who have had a total hysterectomy or bilateral salpingo-oophorectomy

7.3.2 Exclusion Criteria

Individuals who meet any of the following exclusion criteria will not be eligible to participate in the study:

1) Ingestion of N-acetyl-D-mannosamine (ManNAc) or related metabolites; intravenous immunoglobulin (IVIG); or anything that can be metabolized to produce SA in the body within 60 days prior to the Screening Visit
2) Has had any hypersensitivity to SA or its excipients that, in the judgment of the investigator, places the subject at increased risk for adverse effects
3) Pregnant or breastfeeding at Screening or planning to become pregnant (self or partner) at any time during the study
4) Use of any investigational product or investigational medical device within 30 days prior to Screening, or anticipated requirement for any investigational agent prior to completion of all scheduled study assessments
5) Has a condition of such severity and acuity, in the opinion of the investigator, that it warrants immediate surgical intervention or other treatment or may not allow safe participation in the study
6) Has a concurrent disease, active suicidal ideation, or other condition that, in the view of the investigator, places the subject at high risk of poor treatment compliance or of not completing the study, or would interfere with study participation or would affect safety

7.3.3 Removal of Subjects from Therapy or Assessment

In accordance with the Declaration of Helsinki, subjects have the right to withdraw from the study at any time for any reason. The Investigator and Ultragenyx also have the right to remove subjects from the study. Ultragenyx must be notified of all subject withdrawals as soon as possible. Ultragenyx also reserves the right to discontinue the study at any time for either clinical or administrative reasons and to discontinue participation of an individual subject or Investigator due to poor enrollment or noncompliance, as applicable.

Subjects may be removed from the study for the following reasons:

- Occurrence of an unacceptable adverse event (AE)
- A condition or illness that, in the judgment of the Investigator or Ultragenyx, might place the subject at risk or invalidate the study
- At the request of the subject, Investigator, or Ultragenyx, for administrative or other reasons
- Protocol deviation or unreliable behavior

If the reason for removal of a subject from the study is an AE, the AE and any related test or procedure results will be recorded in the source documents and transcribed onto the case report form (CRF). Each clinically significant abnormal laboratory value or other clinically meaningful abnormality should be followed until the abnormality resolves or until a decision is made that it is not likely to resolve. If such abnormalities do not return to normal within 30 days after the last dose given, their etiology should be identified and Ultragenyx should be notified. All unscheduled tests must be reported to Ultragenyx immediately.

If a subject discontinues from the study prematurely, every reasonable effort should be made to perform the Early Termination Visit procedures within four weeks of discontinuation.

7.3.3.1 Stopping Rules

Individual subjects who experience an unexpected and possibly, probably, or definitely drug-related serious adverse event (SAE) (Section 8.5.3) that represents a change in the nature or an increase in frequency of the serious event from their prior medical history or known GNEM-related medical issues will be evaluated as to whether the subject will continue on the study. Periodic safety reviews will be conducted to look at aggregate data on serious adverse event, adverse events, vital signs, and laboratory abnormalities to determine if the study should be stopped.

Regulatory Authorities, as well as the IRBs/ECs, will be informed should unexpected and possibly, probably, or definitely study drug-related SAEs occur. A full evaluation of the event will be performed in order to make a decision regarding what actions to take, including whether to recommend stopping the study. Regulatory Authorities, as well as IRBs/ECs, will be informed if the study is paused or stopped. If the Sponsor deems it appropriate to restart

the trial following an internal safety review, this will be done only following approval by Regulatory Authorities.

7.4 Treatments

Approximately 165 subjects will be eligible to enroll in the study and receive open-label Ace-ER tablets; 6 g/day divided TID.

7.4.1 Investigational Product

Each Ace-ER tablet contains 500 mg of SA in an extended release formulation for a total weight of 1200 mg/tablet. The 6000 mg (6 g) total daily SA dose will be administered by the oral route and will be divided into a TID regimen: 4 tablets taken in the morning, early evening, and before bedtime (qHS). The dose should be administered with food (i.e. within 30 minutes of a meal or snack).

The study drug is manufactured, packaged, and labeled according to current Good Manufacturing Practice (cGMP) regulations.

7.4.2 Reference Therapy

Not applicable.

7.4.3 Selection of Doses and Study Duration

Selection of Doses:

Successful use of SA replacement therapy in humans is believed to depend upon optimized exposure to the compound in the bloodstream to drive uptake of SA into the muscle. The 6 g/day Ace-ER dose was selected based on biochemical and clinical data collected to date showing that 6 g/day is an efficacious dose, that 3 g/day is not efficacious, and that a higher dose of 12 g/day did not result in a significant improvement in effect over 6 g/day. These data derive from a randomized, placebo-controlled Phase 2 study and a corresponding extension study.

Given the biochemical and clinical results from UX001-CL201 and UX001-CL202 (Section 5.2.3), the 6 g/day Ace-ER dose was selected for further study in UX001-CL301 and UX001-CL203; this dose will be continued in the current extension study. All subjects being treated with 12 g/day Ace-ER in UX001-CL202 who rollover will be transitioned to 6 g/day in this protocol.

Study Duration:

The total treatment duration will be 24 months. In addition, a Safety Follow-up visit will be conducted by phone 30 days (+5 days) after the last dose of study drug.

7.4.4 Method of Assigning Subjects to Treatment Groups

This is an open-label study and consists of one treatment arm. All subjects will receive Ace-ER 6g/day.

7.4.5 Blinding

Not applicable.

7.4.6 Prior and Concomitant Therapy

7.4.6.1 Prohibited Medications

Subjects may not be enrolled if they used any investigational product (except for Ace-ER/SA-ER as part of the parent study) or investigational medical device within 30 days prior to Screening, or if they require any investigational agent prior to completion of all scheduled study assessments. Ingestion of ManNAc, SA (other than Ace-ER) or related metabolites, and IVIG are prohibited throughout the study. If ManNAc, SA (other than Ace-ER) or another substrate was used more than 60 days prior to Screening, the time period of use, the compound used, and the dose and dose regimen should be recorded. If a patient has been on substrate replacement therapy in the past, the investigator must consider the potential confounding effects of this therapy before enrolling the patient as a subject in the study.

It is essential that the subject commit to not ingesting ManNAc or similar other SA-producing compounds during the conduct of this study as it could confound the interpretation of the results. The study will analyze subject's urine sample for the presence of ManNAc to detect noncompliance with this essential requirement.

7.4.6.2 Permitted Medications

Other than medications specifically prohibited in this study, subjects may receive concomitant medications as required. Medications (prescription, over-the-counter, and herbal) and nutritional supplements taken during the 30 days prior to Screening will be reviewed and recorded at the Screening visit. At the Baseline visit, current medications will be recorded. At each visit, any concomitant medications added or discontinued during the study should be recorded on the CRF.

The site personnel should record the following in the CRF: date and time the medication was taken, the name of the medication, and the reason the medication was taken.

7.4.7 Treatment Compliance

Site personnel will maintain a record of all medication dispensed to each subject. Subjects will be instructed to bring all unused study drug and product packaging to every visit. Drug accountability will be assessed by site personnel and recorded. All used containers and unused study drug must be returned at in-clinic visits. Measurements of

trough free SA levels in the serum and urine may also provide an estimate of treatment compliance in this study.

7.5 Study Procedures and Assessments

The individual indicated in each scale description will perform all assessments listed below. Whenever possible, study site staff (including trained clinicians, physical therapists, and the Investigator or site designee) performing the assessments should be consistent from visit to visit throughout the study.

The parameters to be assessed in Study UX001-CL302, along with timing of assessments, are provided in the Schedule of Events (Table 2.1). Refer to study-related materials for additional details on specific assessments and the suggested order of administration.

7.5.1 Visit Schedule

Informed consent must be obtained prior to any Screening/Baseline procedures.
Subjects will be enrolled only after inclusion/exclusion criteria have been confirmed.
Screening/Baseline assessments must be completed prior to first dose of study drug.
Study visits will occur at every 8 weeks for 24 weeks and then every 6 months for subjects enrolling from UX001-CL202 or UX001-CL301. For subjects enrolling from study UX001-CL203, study visits will occur every 6 months. A Safety Follow-up visit will be conducted by phone 30 days (+5 days) after the last dose of study drug. For subjects who discontinue prior to completing the study, every reasonable effort should be made to perform the Early Termination Visit procedures within four weeks of discontinuation. Subjects who are unable to return to the clinic will be given the option of having an Early Termination Visit telephone call within 4 weeks of discontinuation from study, where appropriate information will be collected by the clinical site.

7.5.2 Efficacy Measures

Efficacy will be evaluated by changes in upper and lower extremity muscle strength and function, and physical functioning. Results from baseline assessments will be compared with those of post-treatment assessments listed in the Schedule of Events (Table 2.1), with efficacy conclusions based on change from baseline over the treatment period.

The following section describes the assessments that will be performed throughout the study to derive efficacy variables. However, only applicable assessments based on the subject's parent study prior to roll-over should be administered to each subject. For UX001-CL202 subjects, assessments that cannot be safely performed by a subject due to disease progression should not be administered.

7.5.2.1 Dynamometry

Dynamometry testing of multiple muscle groups will be used to measure strength. Dynamometry sessions will occur at each visit beginning with the Screening/Baseline Visit. See Clinical Evaluator Manual for details on the administration procedure of dynamometry.

Formal training will be conducted with the clinicians administering dynamometry (a licensed physical therapist) to standardize technique and minimize variability. The maximum voluntary isometric contraction (MVIC) against a dynamometer will be used to measure strength in the following muscle groups, as applicable: shoulder abductors, elbow flexors, elbow extensors, hip abductors, hip adductors, hip flexors, hip extensors, knee flexors and knee extensors. A hand dynamometer will be used to assess gross grip strength and pinch strength. Refer to the Clinical Evaluator manual for details on the dynamometry testing.

The total force (in kg) will be recorded at the time of test administration. The highest force value collected for each muscle group will be used for data analysis. The percent predicted values will be calculated after the testing using published normative data (Mathiowetz et al. 1985); (NIMS 1996); (Bohannon 1997); (Bohannon et al. 2006); (Peters et al. 2011). Muscle strength and percent predicted values for each muscle group tested will be analyzed as secondary or tertiary endpoints.

7.5.2.1.1 Upper Extremity Composite Score

For UX001-CL202 and UX001-CL301 Subjects: Muscle strength based on the MVIC against a dynamometer will be measured bilaterally in the following upper extremity muscle groups: gross grip, shoulder abductors, elbow flexors, and elbow extensors. The UEC is derived from the sum of the average of the right and left total force values (measured in kg) for each muscle group.

The percent predicted total force values will be determined based on reference equations adjusting for age, gender, height, and weight. The percent predicted force will be calculated for each side and the bilateral percent predicted values will be averaged for each upper extremity muscle group (gross grip, shoulder abductors, elbow flexors, and elbow extensors). The mean of the four averages in percent predicted scores will be calculated to create a percent predicted UEC score, and analyzed relative to baseline to create a UEC mean change in percent predicted score.

For UX001-CL203 Subjects: Muscle strength based on the MVIC against a dynamometer will be measured bilaterally in the following upper extremity muscle groups: grip, key pinch, shoulder abductors and wrist extensors. The UEC is derived from the sum of the average of the right and left total force values (measured in kg) for each muscle group.

The percent predicted total force values will be determined based on reference equations adjusting for age, gender, height, and weight. The percent predicted force will be calculated for each side and the bilateral percent predicted values will be averaged for each upper

extremity muscle group (grip, key pinch, shoulder abductors and wrist extensors). The mean of the four averages in percent predicted scores will be calculated to create a percent predicted UEC score, and analyzed relative to baseline to create a UEC mean change in percent predicted score.

7.5.2.1.2 Lower Extremity Composite Score

For UX001-CL202 and UX001-CL301 Subjects: muscle strength based on MVIC against a dynamometer will be measured bilaterally in the following lower extremity muscle groups: knee flexors, hip flexors, hip extensors, hip abductors and hip adductors. The LEC is derived from the sum of all muscle groups. Each muscle group is the average of the right and left total values (measured in kg).

The percent predicted total force values for the LEC will also be determined and analyzed as a tertiary endpoint. The percent predicted force will be calculated for each side and the bilateral percent predicted values will be averaged for each lower extremity muscle group (knee flexors, hip flexors, hip extensors, hip abductors and hip adductors). The mean of the five averages in percent predicted scores will be calculated to create a percent predicted LEC score, and analyzed relative to baseline to create a LEC mean change in percent predicted score.

7.5.2.1.3 Knee Extensor Score (UX001-CL203)

For UX001-CL203 Subjects: Muscle strength based on MVIC against a dynamometer will be measured bilaterally in the knee extensors muscle group. Lower extremity muscle strength is the average of the right and left total values (measured in kg).

7.5.2.2 GNEM Functional Activities Scale

For UX001-CL202 and UX001-CL301 Subjects: The GNEM-FAS (also referred to as HIBM-FAS in some studies) is a disease-specific measure developed to assess the functional impact of changes in muscle strength. The scale consists of 3 domains: upper extremity, mobility, and self-care; scores for each domain and a total score will be obtained. The scale has been developed specifically for patients with GNEM based on feedback received from affected individuals on the impact of the disease on their function. Items in the scale assess the subject's ability to independently perform various activities of living that involve self-care, mobility and use of the upper and lower extremities. The scale will be administered in an interview format by a trained clinician (preferably a licensed physical therapist) and scored after the testing. The physical therapists' role is a combination of observing subjects conducting activities and asking subjects questions to assess performance of these activities.

For UX001-CL203 Subjects: The original GNEM-FAS was developed as a clinician-reported outcome measure (ClinRO) for ambulatory GNEM patients but has since been modified to a self-report PRO format with items added to accommodate weaker

patients. This modified version is referred to as the GNEM-FAS Expanded Version and will be used for subjects rolling over from the UX001-CL203 study.

7.5.2.3 Sit-to-Stand Test

For UX001-CL202 and UX001-CL301 Subjects: The sit-to-stand test (Agarwal et al. 2006); (Ozalevli et al. 2007) will be administered at Screening for training purposes, and each subsequent scheduled study visit through Week 48 (or Early Termination), to assess lower extremity function. The test will be administered by a trained clinician (preferably a licensed physical therapist). The subject will be asked to stand upright from a seated position in a chair, return to a seated position, and then repeat the sequence at a comfortable pace according to their own rhythm for the 30-second duration of the test. Use of an arm chair or a stationary object for leverage will be permitted if preferred by the subject. The number of times the subject can rise from a seated to a standing position in a 30-second period will be recorded.

The sit-to-stand test will not be performed in subjects who roll-over from the UX001-CL203 study.

7.5.2.4 Weighted Arm Lift Test

For UX001-CL202 and UX001-CL301 Subjects: Upper extremity function will be assessed using a weighted arm lift test. The weighted arm lift test (Agarwal et al. 2006) will be administered at the Screening Visit for training purposes, then at each subsequent scheduled visit through Month 24 (or Early Termination). The subject will be asked to sit in a chair holding a 1 kg barbell with the shoulder adducted, the elbow in full flexion, and the forearm in supination. On command, the subject will be asked to lift the arm above the head until the elbow is fully extended, then to lower the arm back to the starting position. The subject will be asked to repeat the action at a comfortable pace according to their own rhythm for the 30 second duration of the test. The test will be performed bilaterally and the final score will be the mean of the total number of completed repetitions from both arms. The number of times the subject can raise the 1 kg weight above the head in the 30-second test period will be recorded.

The weighted arm lift test will not be performed in subjects who roll-over from the UX001-CL203 study.

7.5.2.5 Six Minute Walk Test

For UX001-CL202 and UX001-CL301 Subjects: The 6MWT will be administered once per test day at each subsequent scheduled study visit through Month 24 (or Early Termination). Refer to study-related materials for detailed instructions on conducting the 6MWT.

The 6MWT will be conducted based on American Thoracic Society guidelines (ATS/ERS 2002). Subjects will be instructed to walk the length of a pre-measured course for

6 consecutive minutes. If applicable, the use of any AFOs and assistive devices in the performance of the 6MWT will be noted. The total distance walked (meters) following the six minute period will be recorded. The percent predicted distance walked (for age and gender) will also be determined based on published normative data (Gibbons et al. 2001).

The six-minute walk test will not be performed in subjects who roll-over from the UX001-CL203 study.

7.5.2.6 Individualized Neuromuscular Quality of Life Questionnaire

For UX001-CL202 and UX001-CL301 Subjects: The Individualized Neuromuscular Quality of Life Questionnaire (INQoL) (Vincent et al. 2007) is an individualized self-report measure of health-related quality of life designed specifically for adults with muscle disease. The INQoL will be presented to the subject in paper format for completion prior to the administration of the performance tests. The INQoL is a 45-item measure consisting of ten subscales; four measure the impact of muscle disease symptoms, including weakness, locking (seizing), pain and fatigue of muscles. Five additional subscales evaluate the degree of symptom impact on particular areas of life, including activities, independence, social, emotional, and body image. The final domain assesses perceived and expected treatment effects and will not be administered due to the blinded nature of the study. All responses are given in a seven-point Likert scale, with higher scores indicating greater impact.

The INQoL will not be performed in subjects who roll-over from the UX001-CL203 or UX001-CL202 studies.

7.5.2.7 Medical Outcomes Survey – 36 Item (SF-36)

For UX001-CL203 Subjects: The SF-36 will be completed by subjects rolling over from the UX001-CL203 study to assess physical and mental health based on 8 scaled scores that are the weighted sums of the questions in their section: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health. Each scale is directly transformed into a 0 to 100 scale on the assumption that each question carries equal weight. Lower scores indicate more diminished health-related quality of life.

The SF-36 will not be performed in subjects who roll-over from the UX001-CL301 or UX001-CL202 studies.

7.5.2.8 Creatine Kinase Levels

CK is a biochemical marker of muscle injury in many muscular system disorders. Most GNEM patients have some modest elevation of CK; in approximately 50% of patients CK levels are increased at least two-fold above the upper limit of normal (ULN). CK levels in serum will be measured as indicated in the Schedule of Events (Table 2.1) to assess the degree of reduction associated with treatment.

7.5.3 Drug Concentration Measurements

The concentration of free SA in serum will be measured to further characterize the PK of Ace-ER. At the Baseline Visit and each subsequent visit a serum sample will be collected, preferably, prior to the morning dose of study medication (pre-dose) to assess trough levels of free SA.

The free, total, and bound urine SA levels (corrected for creatinine) will reflect the absorption of SA and the incorporation into sialylated proteins and oligosaccharides during treatment with Ace-ER tablets. The change in urine SA levels will be analyzed the same as for the primary endpoint. At Baseline/Screening, and each clinic visit, first-morning void urine will be collected (pre-dose) to assess trough levels; the volume obtained will be recorded.

Collection and processing instructions can be found in the Laboratory Manual.

7.5.4 Urine Testing for ManNAc

First morning void urine specimens will be analyzed for the presence of ManNAc at Baseline/Screening, and each clinic visit to detect noncompliance with prohibited medication restrictions. The urine volume obtained will be recorded.

Collection and processing instructions can be found in the Laboratory Manual.

7.5.5 Safety Measures & General Assessments

General assessments include medical history, demographics, height, and weight. Safety will be evaluated by the incidence, frequency and severity of AEs and SAEs, including clinically significant changes from study baseline to scheduled time points in interval history, physical examinations, vital signs, clinical laboratory evaluations, suicidal ideation and behavior, and concomitant medications. Pregnancy testing (or pregnancy of partner, if needed) will also be conducted as appropriate. Refer to study-related materials for additional details on safety measures and general assessments.

7.5.5.1 Medical History

A detailed medical history will be obtained at the Screening/Baseline Visit to solicit information on any prior or existing medical conditions that might interfere with study participation or safety. General medical information includes subject demographics (date of birth, ethnicity, and sex) and a history of major medical illnesses, diagnoses, and surgeries. The GNEM-specific medical history should elicit all major illnesses, diagnoses, and surgeries to date. Any relevant concomitant therapy, including physical/occupational therapy will be recorded.

7.5.5.2 Interval History

The interval history is intended to record any signs, symptoms, or events (e.g. falls) experienced by the subject since the prior study visit that are not related to study procedure(s) performed at prior study visits or study drug. Interval history may include exacerbation or improvement in existing medical conditions (including the clinical manifestations of GNEM) that might interfere with study participation, safety, and/or positively or negatively impact performance of functional assessments. Interval history may identify under-reported AEs and will be collected at each study visit.

7.5.5.3 Physical Examination

Complete physical examinations will be performed at Baseline/Screening.
Physical examinations will include assessments of general appearance; head, eyes, ears, nose, and throat; the cardiovascular, dermatologic, lymphatic, respiratory, GI, genitourinary, musculoskeletal, and neurologic systems. The neurologic system examination will include assessments of cognition, cranial nerves, motor function, coordination and gait, reflexes, and sensory function. Brief physical examinations will be conducted at all other study visits and will include assessments of general appearance, cardiovascular and respiratory systems, and a focus on any presenting complaints. Clinically significant changes from baseline will be recorded as AEs.

7.5.5.3.1 Height and Weight

Height and weight will be captured at the Baseline/Screening Visit and should be measured by the trained clinician administering the performance testing. A stadiometer must be used for all height measurements; if a patient is unable to stand or has significant postural issues that interfere with collection of a standing height, self-reported adult height should be captured. Height should be measured in inches or centimeters without shoes with the subject standing on a flat surface. A calibrated scale must be used for all weight measurements. Weight should be measured in pounds or kilograms without shoes.

Height and weight data will be used to evaluate each subject's muscle strength and function using published normative data where available. The measurement obtained at the Screening/Baseline Visit will be used for all derivations of percent predicted.

7.5.5.4 Vital Signs

Vital signs will include seated systolic blood pressure and diastolic blood pressure measured in millimeters of mercury (mmHg), heart rate in beats per minute, respiration rate in breaths per minute, and temperature in degrees Celsius (°C). Vital signs measurements will be performed at every visit before any additional assessments are completed.

7.5.5.5 Clinical Laboratory Tests for Safety

The clinical laboratory evaluations to be performed in this study include a serum chemistry, complete blood count (hematology), and urinalysis. Specific analytes that will be evaluated are listed in Table 7.5.5.5.1. Clinical laboratory testing will be performed at every visit, except for the safety follow-up call. Blood samples, preferably pre-dose, and first-morning void urine samples will be collected prior to administration of study drug; fasting is not required. Refer to the Laboratory Manual for additional details.

Table 7.5.5.5.1: Clinical Laboratory Assessments for Safety

Chemistry	**Hematology**	**Urinalysis**[+]
Alanine aminotransferase (ALT)	Hematocrit	Appearance
Alkaline phosphatase	Hemoglobin	Color
Amylase	Mean corpuscular hemoglobin (MCH)	pH
Aspartate aminotransferase (AST)	MCH concentration (MCHC)	Specific gravity
Bilirubin (direct and total)	Mean corpuscular volume (MCV)	Ketones
Blood urea nitrogen (BUN)	Platelet count	Protein
Calcium	Red blood cell (RBC) count	Glucose
Chloride	Reticulocyte count	Bilirubin
Cholesterol (total)	Neutrophil count (absolute and %)	Nitrite
Creatine kinase [1]		Urobilinogen
Creatinine	Lymphocyte count (absolute and %)	Hemoglobin
Gamma-glutamyl transpeptidase (GGT)	Monocyte count (absolute and %)	Creatinine [2]
Glucose	Eosinophil count (absolute and %)	ManNAc [3]
Lactate dehydrogenase (LDH)	Basophil count (absolute and %)	Leukocyte esterase
Lipase	White blood cell (WBC) count	Pregnancy test (if applicable)
Phosphorus	WBC differential	Blood/RBC
Potassium		
Protein (albumin and total)		***Special assessment**
Sodium		Serum pregnancy test if a positive urine pregnancy test
Triglycerides		

+ Microscopic examination will be performed only if dip stick is abnormal for protein, leukocyte esterase, blood or nitrite. Microscopic examination may include WBC, RBC, Epithelial Cells, Squamous, Epithelial Cells, Transitional, Epithelial Cells, Renal Tubular, Hyaline Casts, WBC Casts, RBC Casts, Waxy Casts, Granular Casts, Calcium Oxalate Crystals, Uric Acid Crystals, Triphosphate Crystals, Yeast, Bacteria, Amorphous Urates and Amorphous Phosphates

1 Also designated as PD variable (Section 7.5.2.8)

2 Relevant to Drug Concentration Measurements (Section 7.5.3)

3 To screen for use of prohibited medications (Section 7.4.6.1)

Subjects who experience a SAE possibly or probably related to study drug or other AE of concern may, at the discretion of the Investigator (and/or medical monitor), have additional blood samples taken for safety laboratory tests.

Upon completion of protocol-specified laboratory tests, leftover blood and urine samples from each visit may be used for additional exploratory research, eg, biomarker research. The leftover samples from this study will not be used for genetic testing.

7.5.5.5.1 Volume of Blood to Be Drawn from Each Subject

During this study, it is expected that a maximum of approximately 16 mL of blood will be drawn from each subject, at each required time point, regardless of gender or age (Table 7.5.5.5.1.1). The amount of blood to be drawn for each assessment is an estimate, and may vary according to the instructions provided by the manufacturer or laboratory for an individual assessment. Samples indicated at the time point/period may be utilized for more than one assessment if the same type of tube is required (e.g. CK and serum chemistry).

Table 7.5.5.5.1.1: Volume of Blood to Be Drawn From Each Subject

Assessment		Sample Volume (mL)	Number of Samples [2]	Total Volume (mL) [2]
Safety	Chemistry [1]	7.5	7/9	52.5/67.5
	Hematology	3	7/9	21/27
Drug Concentration	Sialic Acid	5	7/7	35/35
Total mL through study completion				108.5/129.5

[1] Includes CK
[2] UX001-CL203 subjects/UX001-CL202 and UX001-CL301 subjects

7.5.5.6 Pregnancy Testing

Female subjects of childbearing potential with a positive pregnancy test at Baseline/ Screening will not be enrolled in the study. Female subjects will have urine pregnancy tests throughout the study.

Additional pregnancy tests will be performed at any visit in which pregnancy status is in question. A serum pregnancy test will be performed in the event of a positive or equivocal urine pregnancy test result, or can be performed if pregnancy test by urine is not feasible.

Experience with UX001 in pregnant women is limited. The study drug may involve risks to a pregnant female or unborn baby which are currently unknown. Participants of child-bearing potential or with partners of child bearing potential who have not undergone a bilateral salpingo-oophorectomy and are sexually active must consent to use a highly effective method of contraception as determined by the site investigator from the period following the signing of the informed consent through 30 days after last dose of study drug. Examples of highly

effective methods of contraception include oral hormonal contraceptives, patch hormonal contraceptives, vaginal ring, intrauterine device, physical double-barrier methods, surgical hysterectomy, vasectomy, tubal ligation or true abstinence (when this is in line with the preferred and usual lifestyle of the subject), which means not having sex for the duration specified above because the subject chooses not to.

7.5.5.6.1 Pregnancy in Subject or Partner

Pregnancies in subjects or partners must be reported within 24 hours of knowledge of the event to Ultragenyx or its designee. The Investigator must make every effort to follow the pregnancy of either subject or partner through resolution of the pregnancy (delivery or termination) and report the resolution to Ultragenyx or its designee. In the event of a pregnancy in the partner of a subject, the Investigator should make every effort to obtain the female partner's consent for release of protected health information. Refer to study-related materials for details on the reporting procedures to follow in the event of pregnancy.

7.5.5.7 Suicidal Ideation and Behavior

Prospective assessment of suicidal ideation and behavior is a regular part of development programs involving any drug being developed for any psychiatric indication, as well as for all antiepileptic drugs and other neurologic drugs with central nervous system activity (Food and Drug Administration [FDA] Draft Guidance, 2012). The C-SSRS is a standardized rating instrument used to assess the suicidal ideation and behavior in an at-risk population (Posner et al. 2011). To prospectively assess suicidal ideation and behavior, the C-SSRS will be administered by trained site personnel. The Baseline/Screening C-SSRS (may be same as last visit in parent study) will be administered at the Screening and Baseline visits; the Since Last Visit C-SSRS will be administered at all subsequent visits.
The responses to the questionnaire will be reviewed by site personnel during the study visit; if emergent suicidal ideation or behavior is indicated, the investigator should promptly evaluate the subject to ensure proper management and protection of subject safety.

7.5.5.8 Concomitant Medications

Concomitant medications will be reviewed and recorded in the subject's CRF at each study visit, beginning at the Screening/Baseline visit. Medications (investigational, prescription, over-the-counter, and herbal) and nutritional supplements taken during the 30 days prior to Screening/Baseline will be reviewed and recorded. At each subsequent visit, change in medications since the previous visit will be recorded. A discussion of concomitant medications is provided in Section 7.4.6.

7.5.5.9 Adverse Events

All AEs will be recorded from the time subjects sign informed consent for this extension study and completion of the End of treatment visit in the parent study until 30 days after the last dose of study drug. Adverse events reported as ongoing at parent study's End of

treatment visit and any new AEs prior to Baseline for this study will be reviewed and recorded at the Baseline visit.

The determination, evaluation, reporting, and follow-up of AEs will be performed as outlined in Section 8.5. At each visit subjects will be asked about any new or ongoing AEs since the previous visit. Assessments of AEs will occur at each study visit.

Clinically significant changes from study baseline in interval history, physical and neurological examination findings, vital signs, weight, clinical laboratory parameters, and concomitant medications will be recorded as AEs or SAEs, if appropriate.

7.5.6 Appropriateness of Measures

There are two different types of patients in this extension study (those with severe ambulatory impairment [UX001-CL203] and subjects from UX001-CL202 and UX001-CL301); specific measures vary depending on their functional status. The efficacy parameters to be evaluated in this study include clinical changes in muscle strength, subject mobility, and function. The clinical assessments in the study employ standard performance measures used in other neuromuscular diseases and conditions that cause muscle weakness and impaired function. Based on results from Phase 2 studies with Ace-ER and published studies in other muscle diseases (Aitkens et al. 1989), the study will focus on quantitative muscle testing. The strength of a set of muscle groups in the upper and lower extremities will be assessed by dynamometry, a form of quantitative muscle testing that uses a device with a strain gauge to measure force during a MVIC (Sisto et al. 2007). The GNEM-FAS will be administered in this study to support the clinical meaningfulness of changes in muscle strength. In addition, walking ability will be assessed using the 6MWT test, a test of endurance commonly used in clinical trials for various indications that has served as the basis for many product approvals.

The level of free SA in serum will reflect the absorption of and exposure of the muscles to SA during treatment. Serum CK level will be assessed as a measure of muscle injury throughout the study; a positive dose-dependent decrease in serum CK levels was observed in the UX001-CL201 Week 24 analysis. Unlike other myopathies, CK activities are mildly elevated or in the normal range for these patients. The mouse model of HIBM showed elevated CK levels that improved substantially on treatment (Malicdan et al. 2009).

The safety parameters to be evaluated in this study include standard assessments such as recording of AEs and SAEs, concomitant medications, medical history, physical examination (including neurological examination), vital signs, serum chemistry, and other routine clinical and laboratory procedures. In addition, symptoms of increasing muscle weakness and pain which are characteristic of myopathy will be recorded in interval histories. Suicidal ideation and behavior will be assessed using C-SSRS, a standardized rating instrument recommended in clinical trials of any investigational drug with potential neurological activity (FDA Draft Guidance, 2012).

7.6 Statistical Methods and Determination of Sample Size

The completeness of the data affects the integrity and accuracy of the final study analysis. Therefore, every effort will be made to ensure complete, accurate and timely data collection, and to avoid missing data. The procedures for handling missing, unused, or spurious data, along with the detailed method for analysis of each variable will be presented in the Statistical Analysis Plan (SAP); the information below is intended as a guide to planned analyses.

7.6.1 Determination of Sample Size

The current study is primarily designed to evaluate safety and the sample size is intended to provide the maximum amount of information regarding UX001 tolerability along with indicators of long-term safety and efficacy in this patient population. Approximately 165 adult subjects with GNEM are expected to roll-over from UX001-CL202 (N=55), UX001-CL301 (N=80), and UX001-CL203 (N=30) studies to participate in this extension study.

7.6.2 Subject Information

Summaries and listings will be provided for all subjects who received at least 1 dose of study drug and provided at least 1 safety or efficacy evaluation. Subject disposition summaries will include the number of enrolled subjects, the number of subjects receiving study medication, the number of subjects completing the study, and the reasons for discontinuation. Demographic variables include age, sex, and race.

7.6.3 Populations Analyzed

Full Analysis Set: The full efficacy set will include all subjects with a baseline measurement and at least one post-baseline measurement. This set will be used for the primary analyses of all efficacy endpoints.

Safety Analysis Set: The safety analysis set consists of all subjects who receive at least one dose of study drug. This set will be used for the analyses of all safety endpoints.

Sialic Acid Analysis Set: The SA analysis set will consist of all randomized subjects with evaluable free serum SA levels.

7.6.4 Efficacy Analysis

Separate analyses will be performed for subjects coming from each parent study.

The full analysis set will include all subjects with a baseline measurement and at least one post-baseline measurement. This set will be used for the analyses of all efficacy endpoints.

Baseline values for each endpoint will be defined as the last scheduled data collection visit before first dose according to the Schedule of Events (Table 2.1).

Efficacy analyses will use generalized estimating equation (GEE) to evaluate trends over time with respect the changes from baseline for the primary efficacy endpoint, and all secondary and tertiary efficacy endpoints. Baseline will be included as a covariate in the model. This method will be the primary analysis method for all repeated measures endpoints.

The statistical analyses will be reported using summary tables, figures, and data listings.

Statistical tests will be 2-sided at the alpha=0.05 significance level.

Continuous variables will be summarized with means, standard deviations, medians, minimums, and maximums. Categorical variables will be summarized by counts and by percentages of subjects in corresponding categories.

7.6.5 Analyses of Drug Concentration Measurements

The SA analysis set will be used to evaluate free serum SA levels and urine SA levels (free, bound and total; corrected for creatinine) at trough (pre-dose) using the SA analysis set. Changes from baseline will be analyzed using the GEE method for repeated measures analysis.

7.6.6 Safety Analyses

Safety will be evaluated for the overall study population as well as for subjects from the UX001-CL202, UX001-CL301, and UX001-CL203 study.

The safety analysis set will be used for the analyses of all safety endpoints. Safety will be evaluated by the incidence, frequency and severity of AEs and SAEs, and clinically significant changes from study baseline to scheduled time points in:

- Interval history
- Vital signs
- Physical examination findings
- Clinical laboratory evaluations
- Suicidal ideation and behavior assessments (C-SSRS)
- Concomitant medications

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence and frequency of AEs will be summarized by System Organ Class (SOC), Preferred Term (PT), severity, and relationship to treatment. The numbers (frequency) and incidence rates of AEs and SAEs will be summarized by treatment group. A by-subject listing will be provided for those subjects who experience a SAE, including death, or experience an AE associated with early withdrawal from the study or study drug treatment.

Clinical laboratory data will be summarized by the type of laboratory test. The frequency and percentage of subjects who experience abnormal clinical laboratory results (i.e. outside of reference ranges) and/or clinically significant abnormalities will be presented for each clinical laboratory measurement. For each clinical laboratory measurement, descriptive statistics will be provided for study baseline and all subsequent post-treatment scheduled visits. Changes from study baseline to the post-treatment visits will also be provided.

Changes in findings from study baseline physical examinations will be tabulated for each subject by examination category. If there are examination findings that change in more than one subject, these will be tabulated in a separate table and expressed as the number of subjects with the change out of the total. No statistics will be applied to the physical examination findings.

The SAP will provide additional details on the planned safety analyses.

8 STUDY CONDUCT

8.1 Ethics

8.1.1 Institutional Review Board or Ethics Committee

The Institutional Review Board (IRB)/Ethics Committee (EC) must be a properly constituted board or committee operating in accordance with 21 Code of Federal Regulations (CFR) Part 56, "Institutional Review Boards." This protocol, any protocol amendments, and the associated informed consent forms (ICFs) must be submitted to the IRB/EC for review and must be approved before screening of any subject into the study. Study drug may not be shipped to the Investigator until Ultragenyx or its designee has received a copy of the letter or certificate of approval from the IRB/EC for the protocol and any protocol amendments, as applicable.

All subject recruitment and/or advertising information must be submitted to the IRB/EC and Ultragenyx or its designee for review and approval prior to implementation. IRB/EC approval of any protocol amendments must be received before any of the changes outlined in the amendments are put into effect, except when the amendment has been enacted to protect subject safety. In such cases, the chair of the IRB/EC should be notified immediately and the amendment forwarded to the IRB/EC for review and approval.

8.1.2 Ethical Conduct of Study

This protocol is written 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 Sponsor and Investigator will make every effort to assure the study described in this protocol is conducted in full conformance with those principles, current FDA regulations, ICH Good Clinical Practices (GCP) guidelines, and local ethical and regulatory requirements. Should a conflict arise, the Sponsor and Investigator will follow whichever law or guideline affords the greater protection to the individual subject. The investigator will also make sure he or she is thoroughly familiar with the appropriate administration and potential risks of administration of the study drug, as described in this protocol and the IB, prior to the initiation of the study.

8.1.3 Subject Information and Consent

Appropriate forms for documenting written informed consent will be provided by the Investigator and reviewed and approved by Ultragenyx or its designee before submission to the IRB/EC. Ultragenyx or its designee must receive a copy of the IRB/EC's approval of the informed consent form (ICF) before the shipment of study drug to the study site.

It is the Investigator's responsibility to obtain signed written informed consent from each potential study subject prior to the conduct of any study procedures. This written informed consent will be obtained after the methods, objectives, requirements, and potential risks of the study have been fully explained to each potential subject. The Investigator must explain

to each subject that the subject is completely free to refuse to enter the study or to withdraw from it at any time.

The method of obtaining and documenting informed consent and the contents of the ICF will comply with ICH GCP guidelines, the requirements of 21 CFR Part 50, "Protection of Human Subjects," the Health Insurance Portability and Accountability Act (HIPAA) regulations, and all other applicable regulatory requirements. Subjects will be given a copy of the signed ICF and will be provided any new information during the course of the study that might affect their continued participation in the study. The Investigator or a qualified designee will be available to answer each subject's questions throughout the study, and all of the subject's questions must be answered to the subject's satisfaction. If the protocol is amended and the ICF is revised, each subject will be required to provide written informed consent again using the revised ICF.

The date of written informed consent will be documented in each potential subject's CRF. The signed ICF will remain in each subject's study file and must be available to the study monitor(s) at all times.

8.2 Investigators and Study Administrative Structure

Each Investigator must provide Ultragenyx and/or its designee a completed and signed Form FDA 1572 and a Financial Disclosure Form. All sub-investigators must be listed on Form FDA 1572 and Financial Disclosure Forms must be completed for all sub-investigators listed on Form FDA 1572.

Ultragenyx and/or its designee will be responsible for managing and monitoring the clinical trial to ensure compliance with FDA and ICH GCP guidelines. Ultragenyx's trained designated representative (the monitor) will conduct regular visits to the clinical site to perform source document verification. The monitor will verify the Investigator's ongoing qualifications, inspect clinical site facilities, and inspect study records, including proof of IRB/EC review, with the stipulation that subject confidentiality will be maintained in accordance with local and federal regulations, including HIPAA requirements.

A Coordinating Investigator will be identified for multicenter trials. The Coordinating Investigator will be selected on the basis of active participation in the trial, thorough knowledge of the therapeutic area being studied, and the ability to interpret data. The Coordinating Investigator will read and sign the Clinical Study Report (CSR).

8.3 Investigational Product Accountability

While at the clinical site, study drug must be stored in a secure limited access location at controlled temperature as described in the IB and according to product packaging. The storage facility must be available for inspection by the study monitor at any time during the study.

A drug accountability record must be maintained for all study drug received, dispensed, returned, and/or lost during the study. This record must be kept current and made available to the study monitor for inspection. Following the close-out of the study, all unused study drug must be returned to Ultragenyx and/or its designee unless other instructions have been provided for final disposition of the study drug.

8.4 Data Handling and Record Keeping

8.4.1 Case Report Forms and Source Documents

The Investigator is required to initiate and maintain, for each subject, an adequate and accurate case history that records all observations and other data related to the study for that subject. A validated electronic data capture (EDC) system will be used for entry of the data into electronic CRFs. Data must be recorded on CRFs approved by Ultragenyx or its designee. All information recorded on CRFs for this study must be consistent with the subject's source documentation.

Initial data entry and any changes to the data will be made only by Ultragenyx-authorized users, and data entries and changes will be captured in an electronic audit trail.
An explanation of any data change should be recorded in the CRF. All data entered in to the CRF must be verifiable; therefore, CRFs will be routinely checked for accuracy, completeness, and clarity and will be cross-checked for consistency with source documents, including laboratory test reports and other subject records by Ultragenyx or its designee.
The Investigator must allow direct access to all source documents.

8.4.2 Data Quality Assurance

Monitoring and auditing procedures developed by Ultragenyx and/or its designee will be implemented to ensure compliance with FDA and ICH GCP guidelines. Ultragenyx's designated representative (the monitor) will contact the Investigator and conduct regular visits to the study site. The monitor will be expected and allowed to verify the Investigator's qualifications, to inspect clinical site facilities, and to inspect study records, including proof of IRB/EC review, with the stipulation that subject confidentiality will be maintained in accordance with local and federal regulations, including HIPAA requirements. The monitor will also be responsible for confirming adherence to the study protocol, inspecting CRFs and source documents, and ensuring the integrity of the data. CRFs will be checked for accuracy, completeness, and clarity and will be cross-checked for consistency with source documents including progress notes, laboratory test reports and other subject records. Instances of missing or uninterruptable data will be resolved in coordination with the Investigator.

The monitor will also investigate any questions concerning adherence to regulatory requirements. Any administrative concerns will be clarified and followed. The monitor will maintain contact with the site through frequent direct communications via e-mail, telephone, facsimile, and/or mail. The Investigator and all other site personnel agree to cooperate fully with the monitor and will work in good faith with the monitor to resolve any and all questions raised and any and all issues identified by the monitor.

The Investigator understands that regulatory authorities, the IRB/EC, and/or Ultragenyx or its designees have the right to access all CRFs, source documents, and other study documentation for on-site audit or inspection and will retain this right from the start of the study to at least two years after the last approval of a marketing application or for at least two years after clinical development of the study drug for the indication being studied has been discontinued. The Investigator is required to guaranty access to these documents and to cooperate with and support such audits and inspections.

8.4.3 Record Retention

All study records must be retained for at least 25 years after the end of the clinical trial or in accordance with national law. Subject files and other source data must be kept for the maximum period of time permitted by the hospital, institution or private practice, but not less than 25 years. Ultragenyx must be notified and will assist with retention should the Investigator/institution be unable to continue maintenance of subject files for the full 25 years. All study records must be stored in a secure and safe facility.

8.5 Reporting and Follow-up of Adverse Events

8.5.1 Definition of Adverse Events

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) products.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of expedited safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

Life-threatening AE or life-threatening suspected adverse reaction is an AE or suspected adverse reaction that, in the view of either the Investigator or Ultragenyx, places the patient or subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the current Investigators Brochure's Reference Safety Information (RSI) or is not listed at the specificity or severity that has been observed.

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)
- A congenital anomaly/birth defect

Note that hospitalizations planned prior to study enrollment (e.g. for elective surgeries) are not considered SAEs. Hospitalizations that occur for pre-existing conditions that are scheduled after study enrollment are considered SAEs.

Important medical events that may not result in death, be immediately life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

8.5.2 Severity of Adverse Events

Wherever possible, the severity of all AEs will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE; version 4.03).
The majority of AEs can be graded using this system.

If an AE cannot be graded using the CTCAE criteria, it should be graded as mild, moderate, severe, life-threatening, or death using the following definitions.

- Mild (Grade 1): Awareness of signs or symptoms, but easily tolerated and of a minor irritant type, causing no loss of time from normal activities. Symptoms do not require therapy or a medical evaluation; signs and symptoms are transient.
- Moderate (Grade 2): Events introduce a low level of inconvenience or concern to the participant and may interfere with daily activities, but are usually improved by simple therapeutic measures; moderate experiences may cause some interference with functioning.
- Severe (Grade 3): Events interrupt the participant's normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating.
- Life-threatening (Grade 4): Events that place the participant at immediate risk of death or are disabling.
- Death (Grade 5): Events that result in death.

To make sure there is no confusion or misunderstanding of the difference between the terms "serious" and "severe," which are not synonymous, the following note of clarification is provided. The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious" which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

8.5.3 Relationship of Adverse Events to Study Drug

The Investigator will assess the potential relationship of the AE to study drug using the following descriptions.

Categories of attributions for "Unrelated" events:

- ***Unrelated:*** This category applies to an AE that ***is clearly not related*** to the investigational agent/procedure.
- ***Unlikely Related:*** This category applied to an AE that ***is doubtfully related*** to the investigational agent/procedure.

Categories of attributions for "Related" events:

- ***Possibly Related:*** This category applies to an AE that ***may be related*** to the investigational agent/procedure.
- ***Probably Related:*** This category applies to an AE that ***is likely related*** to the investigational agent/procedure.
- ***Definitely Related:*** This category applies to an AE that ***is clearly related*** to the investigational agent/procedure.

For the purposes of reporting to regulatory agencies, AEs deemed as Definitely, Probably or Possibly Related will be considered Related and those deemed Unrelated or Unlikely Related will be considered Unrelated.

8.5.4 Adverse Event Reporting

8.5.4.1 General

All AEs (i.e. any new or worsening in severity or frequency of a preexisting condition) with onset after the subject signs consent for study participation must be promptly documented on the CRF. The Principal Investigator is responsible for evaluating all AEs, obtaining supporting documents, and ensuring documentation of the event is adequate. Details of the AE must include severity, relationship to study drug, duration, and outcome.

All AEs will be recorded from the time subjects sign informed consent for this extension study and completion of the End of treatment visit in the parent study until 30 days after the

last dose of study drug. Adverse events reported as ongoing at parent study's End of treatment visit and any new AEs prior to Screening /Baseline visit for this study will be reviewed and recorded at the Screening/Baseline visit.

In addition, the Investigator should report any AE that occurs after this time period that is believed to have a reasonable possibility of being associated with study drug.

AEs ongoing at 30 days following the last dose of study drug should have a comment in the source document by the Investigator that the event has recovered, recovered with sequelae, or stabilized.

8.5.4.2 Serious Adverse Events, Serious Adverse Drug Reactions, and Requirements for Immediate Reporting

Ultragenyx or its designee must be notified of the occurrence of any SAE that occurs during the reporting period within 24 hours of the Investigator, designee, or site personnel's knowledge of the event. SAEs will be reported by completing and submitting SAE report forms to Ultragenyx or designee.

Follow-up SAE information must be submitted in a timely manner as additional information becomes available. All SAEs regardless of relationship to study drug must be followed to resolution or stabilization if improvement is not expected.

All deaths, regardless of causality, occurring from signing of the informed consent until 30 days following the last dose of study drug are to be reported as SAEs to Ultragenyx or its designee within 24 hours of knowledge.

8.5.4.3 Pregnancy Reports

Reported pregnancy of a subject or a subject's partner, while participating in the study, will be monitored for the full duration and/or followed until the outcome of the pregnancy is known. Pregnancy associated SAEs will be processed and submitted, as necessary, as per the suspected unexpected serious adverse reactions (SUSAR) reporting process indicated in Section 8.5.5.1.

8.5.5 Communication Plan

8.5.5.1 Adverse Drug Reaction Reporting

Ultragenyx or its designee will submit SUSAR to appropriate Regulatory Authorities (including Competent Authorities in all Member States concerned), ECs, and Investigators as per local laws and regulations. Fatal and life-threatening SUSARs will be submitted no later than 7-calendar days of first knowledge of the event and follow-up information submitted within an additional eight (8) days. All other SUSARs will be submitted within 15-calendar days of first knowledge of the event.

Principal Investigators are required to report any urgent safety matters to Ultragenyx or its designee within 24 hours. Ultragenyx or its designee will inform the Regulatory Authorities, ECs, and Investigators of any events (e.g. change to the safety profile of SA, major safety findings) that may occur during the clinical trial that do not fall within the definition of a SUSAR but may affect the safety of subjects participating in the clinical trials, as required, in accordance with applicable laws and regulations. The reporting period for urgent safety issues is the period from the signing of the ICF through 30 days following the last dose of study drug.

The Investigator will notify the IRBs/Research Ethics Boards (REB)/ECs of SAEs and urgent safety matters, in accordance with IRB/REB/EC requirements and local laws and regulations. A copy of this notification must be provided to Ultragenyx or its designee.

Non-SUSARs will be maintained in the Ultragenyx safety database and provided in annual and/or periodic reports as per local laws and regulations. Ultragenyx or its designee will prepare and submit annual safety reports and/or other aggregate periodic summary reports to Regulatory Authorities and ECs, as per local laws and regulations.

8.5.6 Urgent Safety Measures

The regulations governing clinical studies state that the Sponsor and Investigator are required to take appropriate urgent safety measures to protect subjects against any immediate hazards that may affect the safety of subjects, and that the appropriate regulatory bodies should be notified according to their respective regulations. According to the European Union (EU) Clinical Trial Directive 2001/20/EC, "…in the light of the circumstances, notably the occurrence of any new event relating to the conduct of the trial or the development of the investigational medicinal product where that new event is likely to affect the safety of the subjects, the Sponsor and the Investigator shall take appropriate urgent safety measures to protect the subjects against any immediate hazard. The Sponsor shall forthwith inform the competent authorities of those new events and the measures taken and shall ensure that the EC is notified at the same time." The reporting period for urgent safety measures is the period from the signing of the ICF through completion of the last study visit. Investigators are required to report any urgent safety measures to Ultragenyx within 24 hours.

8.5.7 Safety Contact Information

Drug Safety	Medical Monitor
PrimeVigilance Fax: [redacted] e-mail: [redacted]	Ed Conner, MD Telephone: [redacted] e-mail: [redacted]

8.6 Financing and Insurance

Financing and insurance for this clinical trial will be addressed in clinical trial agreements with the study site.

8.7 Publication Policy

Any publication or presentation by the Investigator and/or the Institution based on data or results resulting from the Ultragenyx study shall only be done in strict accordance with the Publication section in the Clinical Trial Agreement executed between Ultragenyx and the Institution and/or the Investigator.

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10 SIGNATURE PAGE

Protocol Title: A Phase 3b Open-label 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)

Protocol Number: UX001-CL302, Amendment 1

I have read Protocol UX001-CL302, Amendment 1. I agree to conduct the study as detailed in this protocol and in compliance with the Declaration of Helsinki, Good Clinical Practices (GCP), and all applicable regulatory requirements and guidelines.

Investigator Signature Date

Printed Name: _____

Accepted for the Sponsor:

As the Sponsor representative, I confirm that Ultragenyx will comply with all Sponsor obligations as detailed in all applicable regulations and guidelines. I will ensure the Investigator is informed of all relevant information that becomes available during the conduct of this study.

[redacted] [redacted]

Ed Conner, MD Date
Vice President, Clinical Science
Ultragenyx Pharmaceutical Inc.