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

Protocol Number: UX001-CL203

Original Protocol: 04 December 2015

Amendment 1: 15 March 2017

Investigational Product:	Aceneuramic Acid Extended-Release (Ace-ER) Tablets
Indication:	Treatment of GNE myopathy (GNEM), also known as hereditary inclusion body myopathy (HIBM)
IND/EudraCT Number:	109,334 / 2015-004553-41
Sponsor:	Ultragenyx Pharmaceutical Inc. 60 Leveroni Court Novato, CA 94949 USA
Sponsor's Responsible Medical Officer:	Hank Mansbach, M.D. Vice President, Global Medical Affairs Ultragenyx Pharmaceutical Inc. 60 Leveroni Court Novato, CA 94949 USA PPD
Coordinating Investigator:	Tahseen Mozaffar, M.D. University of California, Irvine

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-CL203 Amendment 1

15 March 2017

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

1. Section 2 (Synopsis), Section 7.1 (Overall Study Design and Plan), Section 7.4 (Treatments), and Section 7.6.1 (Determination of Sample Size) were updated to indicate that approximately 45 subjects are planned for enrollment, rather than 30. Statements about the probability of observing one or more serious adverse events in the study based on the planned sample size were consequently also updated.

   Rationale: This change was made to enable enrollment of additional subjects identified as potentially eligible for this study.

2. Table 2.1 (Schedule of Events) and Section 7.4.2 (Selection of Doses and Study Duration) were updated and Section 7.5.1.5 (Safety Follow-up Period) was added to clarify that a Safety Follow-up telephone call (TC) should be conducted for subjects who complete the study and choose not to enroll in the extension study, UX001-CL302, or who discontinue the study early. This TC should be conducted 30 (+5) days after the last dose of study drug for subjects who complete the study or 30 (+5) days after the ET Visit or TC for subjects who discontinue the study early. Information on ongoing or new adverse events, serious adverse events, and concomitant medications will be collected.

Within Table 2.1, this involved adding a new column for this Safety Follow-up and a new footnote.

Rationale: This change was made to clarify the Safety Follow-up.

3. In Table 2.1 (Schedule of Events) and Section 7.5 (Study Procedures and Assessments), the instruction, "Study assessments for a subject should be performed in a consistent order at each visit," was added. In the table, this was included as a new footnote. The statement, "Refer to the Clinical Evaluator Manual for additional details on specific assessments and the suggested order of administration," which was already in Section 7.5, was also included in this new footnote.

   Rationale: This change was made to ensure that the order of assessments is consistent at each visit yet allow flexibility in the order that the assessments are performed, because the order of assessments should not affect overall study results if it is consistent across visits for an individual subject.

4. In Table 2.1 (Schedule of Events) and Section 7.5.2.6 (Clinical Laboratory Tests for Safety), the following changes were made:

   a. A requirement to perform urine microscopic examination if urinalysis detects protein, leukocyte esterase, blood, or nitrite was added. Within Table 2.1, this involved adding a new footnote to specify this requirement.

      Rationale: This change was made to ensure that that microscopic evaluation will be conducted when abnormal urinalysis results are observed.

   b. The requirement to collect blood and urine samples after administration of hand-held dynamometry assessments and prior to administration of study drug was removed. Within Table 2.1, this involved removal of the footnote specifying this requirement.

      Rationale: This change was made to align with change #3.

5. In Table 2.1 (Schedule of Events) and Section 7.5.3.3, instruction that the SF-36 will only be completed for subjects when a validated version is available in the subject's native language was added.

   Rationale: This change was made because a validated version of the SF-36 is not currently available in the native language of all subjects in this study. Therefore, this self-reported instrument will only be administered for those for whom it is available in their native language.

6. In Table 2.1 (Schedule of Events) and Section 7.5.4 (Drug Concentration Measurements), the requirement for collection and assessment of first morning void urine SA concentration was removed. Consequently, description of analysis of urine SA concentration was removed from Section 2 (Synopsis) and Section 7.6.5.

   Rationale: This change was made to decrease the burden of assessments for subjects, because assessment of serum SA concentration is being performed and additional urine SA data from first morning void urine is unlikely to further inform the PK or PK/PD profile of aceneuramic acid in these subjects.

7. In Table 2.1 (Schedule of Events) and Section 7.5.5 (Urine Testing for ManNAc), instruction that an aliquot from the urine sample provided for the standard urinalysis testing will be used for assessment of ManNAc throughout the study was added. Within Table 2.1, this involved adding a new footnote specifying this. In Section 7.5.5, this addition replaced the requirement for first morning void collection of urine for assessment of ManNAc.

   Rationale: This change was made to clarify that urine for assessment of the presence of ManNAc will come from the safety urinalysis sample, rather than from the first morning void.

8. Table 2.1 (Schedule of Events) was updated to indicate that general medical history, height, and weight should not be collected at the Baseline Visit (only at the Screening Visit) and that interval history should be assessed at the Baseline Visit rather than the Screening Visit.

   Rationale: This change was made to align the timing of collection of general medical history, height, and weight and of the interval history assessment between the schedule of events and Section 7.5.2.

9. Within Section 7.3.2 (Exclusion Criteria), the exclusion criteria numbering was updated.

   Rationale: This change was made to make the exclusion criteria numbering in this section consistent with that in the Synopsis.

10. Section 7.3.3 (Removal of Subjects from Therapy or Assessment), Section 7.5.2.10 (Adverse Events), Section 8.5.4.1 (General), Section 8.5.4.2 (Serious Adverse Events, Serious Adverse Drug Reactions, and Requirements for Immediate Reporting), Section 8.5.5.1 (Adverse Drug Reaction Reporting), and Section 8.5.6 (Urgent Safety Measures) were updated to clarify the end of the data collection period for safety reporting.

    Rationale: This change was made to clarify the safety reporting period for all subjects who take part in the study.

11. Section 7.4.4.1 (Prohibited Medications) was updated to replace the specification that subjects may not be enrolled if they have a history of more than 30 days treatment with SA in the past year with the specification that subjects may not be enrolled if they participated in another aceneuramic acid study involving treatment with Ace-ER/placebo and/or SA-IR in the past year.

    Rationale: This change was made to align Section 7.4.4.1 with the study exclusion criteria.

12. Within Section 7.5.1 (Study Schedule), the following changes were made:

    a. The following statement was added: "The Schedule of Events (Table 2.1) details all procedures to be completed at each visit and should serve as the primary section of the protocol regarding visit-specific study procedures."

       Rationale: This statement was added to specify that the Schedule of Events serves as the primary reference regarding the procedures to be performed at each study visit.

    b. The content was reorganized and divided into subsections comprising Sections 7.5.1.1 (Screening Period), 7.5.1.2 (Baseline Visit), 7.5.1.3 (Treatment Period), 7.5.1.4 (End of Study/Early Termination Visit), and 7.5.1.5 (Safety Follow-up Period).

       Rationale: This reorganization and division was done to more clearly delineate the study periods/visits.

    c. Within the new Sections 7.5.1.1, 7.5.1.4, and 7.5.1.5 specified above, additional information clarifying visit requirements was provided.

       Rationale: These changes were made to more clearly define the study period/visits and the associated assessments. In particular, Section 7.5.1.5 incorporated the information about the Safety Follow-up described in Change 2 above.

    d. Within new Section 7.5.1.2, the timeframe for conduct of the Baseline Visit relative to the Screening Visit was modified from a requirement to a guideline.

       Rationale: This change was made to allow flexibility if needed for scheduling purposes.

13. In Section 7.5.2 (Safety Measures and General Assessments), the statement, "Refer to the Study Reference Manual for additional details on safety measures and general assessments" was removed.

    Rationale: This change was made because the Study Reference Manual will no longer be used for the UX001-CL203 study. Because the safety reporting information provided in the manual is already provided in the study protocols, the manual is not necessary. Discontinuing use of the manual will avoid presentation of inconsistent information across study documents by eliminating documents that have redundant content.

14. In Section 7.5.2.5, the instruction that vital signs measurements will be performed before any additional assessments are completed was removed.

    Rationale: This change was made to align with change #3.

15. In Section 7.5.2.6 (Clinical Laboratory Tests for Safety), Table 7.5.2.6.1 was updated to include blood/RBC and leukocyte esterase in the urinalysis assessments and to present analytes in alphabetical order. In addition, the following text was added to the section: "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."

    Rationale: The table was updated to reflect tests to be performed and for ease of use. The text was added to clarify what may be done with leftover blood and urine samples from this study for subjects who have provided consent for the use of the leftover samples for future research.

16. In Section 7.5.2.6.1 (Volume of Blood to Be Drawn from Each Subject), Table 7.5.2.6.1.1 was updated to indicate that the sample volume of blood drawn for serum SA testing is 5 mL and the overall volume of blood that will be obtained during the study is 88 mL.

    Rationale: This change was made to correctly reflect the total blood volume required to ensure a primary and back-up serum sialic acid sample are obtained.

17. In Section 8.4.3 (Record Retention), the minimum retention period for subject identifier, subject files, and other source data was increased from 15 to 25 years after the completion or discontinuation of the study.

    Rationale: This change was made to align with current regulatory requirements.

18. The title page was updated to include Dr Hank Mansbach as the Sponsor's Responsible Medical Officer and Dr Tahseen Mozzafar as the Coordinating Investigator for this study. Also, Section 8.5.7 (Safety Contact Information) was updated with Dr Hank Mansbach's information.

2 SYNOPSIS

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

PROTOCOL NUMBER:
UX001-CL203

STUDY SITES:
Approximately 8 sites in U.S., Canada, and Bulgaria

PHASE OF DEVELOPMENT:
Phase 2

RATIONALE:
GNEM (or HIBM), is a rare, severely debilitating disease of adult onset myopathy and progressive muscle weakness 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 reduced SA and the resulting reduction of 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 tablets), given SA's short half-life. A Phase 2, randomized, double-blind, 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 better preserved muscle strength compared with placebo or the lower 3 g/day Ace-ER dose. This finding was supported by measurements of functional outcome on GNE Myopathy Functional Activities Scale (GNEM-FAS). Based on these results, a Phase 3 study is being conducted to confirm, and further evaluate the efficacy of Ace-ER 6 g/day in preserving upper extremity muscle strength and function (UX001-CL301). The primary objective of this Phase 2 study is to evaluate the safety of open-label 6 g/day Ace-ER in GNEM subjects with severe ambulatory impairment. The study will also assess efficacy to ensure that the full spectrum of patients with GNEM are evaluated.

For the purposes of this study, a subject with severe ambulatory impairment is defined as:

- Unable to rise from a seated position to standing without help from another person, assistive device(s), stationary object, or other support

  AND

- Unable to walk without the assistance of another person OR if able to walk (use of assistive device(s) permitted), requires at least 2 minutes to walk 40 meters (one full lap of the Six Minute Walk Test (6MWT) course)

  AND

- Use of wheelchair or scooter for activities outside of the home or unable to leave the home independently

OBJECTIVES:

Primary Objective: Evaluate the safety of Ace-ER in GNEM subjects with severe ambulatory impairment

Secondary Objectives: Evaluate the efficacy of 6 g/day Ace-ER in GNEM subjects with severe ambulatory impairment

Exploratory Objectives: Evaluate the effect of 6g/day Ace-ER on health-related quality of life (HRQoL), patient reported outcomes (PRO), and biomarkers of sialyation.

ENDPOINTS:

Primary Endpoint:

The primary endpoint of the study is the incidence and frequency of adverse events (AEs) and serious adverse events (SAEs) assessed as related to Ace-ER over the duration of the study.

Secondary Endpoints:

Safety Endpoints:

- Clinically significant changes from baseline to scheduled time points in concomitant medications, physical examination results, vital signs, clinical laboratory results and interval history during the course of the study

Clinical Endpoints:

- Change in GNEM-FAS Expanded Version total score and mobility, upper extremity and self-care domain scores from baseline over the duration of the study
- Change in upper extremity strength in the following muscle groups: grip, key pinch, shoulder abductors and wrist extensors as measured by dynamometry over the duration of study
- Change in lower extremity muscle strength in the knee extensors as measured by dynamometry over the duration of the study

Exploratory Endpoints:

The exploratory endpoints of the study include HRQoL, patient reported outcomes and biomarker analyses.

- Change in health-related quality of life as assessed by using Short Form Health Survey -36 (SF-36) over the duration of the study
- Change in symptom severity as measured by Patient Global Impression of Severity (PGI-S) and Patient Global Impression of Change (PGI-C) over the duration of the study
- Changes in serum creatine kinase (CK) as a marker of muscle injury over the duration of the study
- Changes in biomarkers of sialylation

STUDY DESIGN AND METHODOLOGY:

This is an open-label, multi-center study to assess the safety of Ace-ER in GNEM patients with severe ambulatory impairment. Efficacy will also be assessed as a secondary objective. Approximately 45 subjects will be enrolled in the study and receive 6 g/day Ace-ER for 48 weeks.

Subjects will take 4 tablets (500 mg 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). Treatment will be administered for a total of 48 weeks. Study visits will occur every 12 weeks during the Treatment

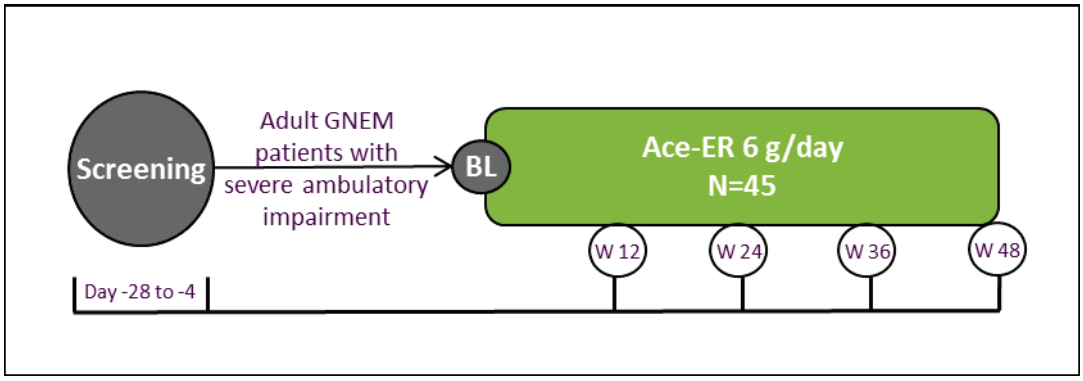
Period during which the scheduled assessments will be administered as outlined in the Schedule of Events (Table 2.1).

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, concomitant medications, and suicidal ideation and behavior (assessed using the Columbia Suicide Severity Rating Scale [C-SSRS]).

Information on biomarkers will be collected to assess their value in predicting clinical severity and disease progression, as well as the ability to determine the long-term impact of disease-targeted treatments and therapies for GNEM.

Efficacy will be evaluated by dynamometry as a measure of muscle strength and patient-reported outcome measures as measures 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 45 adult GNEM subjects with severe ambulatory impairment are planned for the study.

DIAGNOSIS AND CRITERIA FOR INCLUSION AND EXCLUSION:

The criteria below should be applied to all subjects who are screened for the study

INCLUSION CRITERIA

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

1. Male or female, aged ≥ 18 years old
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. Have a documented diagnosis of GNEM, HIBM, distal myopathy with rimmed vacuoles (DMRV), or Nonaka disease due to previously demonstrated mutations in the gene encoding the GNE/MNK enzyme (genotyping will not be conducted in this study).
4. Should meet the criteria for severe ambulatory impairment defined below:
   - Unable to rise from a seated position to standing without help from another person, assistive device(s), stationary object, or other support

AND

- Unable to walk without the assistance of another person OR if able to walk (use of assistive device(s) permitted), requires at least 2 minutes to walk 40 meters (one full lap of the 6MWT course)

  AND

- Use of wheelchair or scooter for activities outside of the home or unable to leave the home independently

5. Willing and able to comply with all study procedures
6. 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 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
7. 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

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), SA, 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. Prior participation in a clinical trial involving treatment with Ace-ER/placebo and/or Sialic Acid-immediate release (SA-IR) in the past year
3. Has had any hypersensitivity to aceneuramic acid or its excipients that, in the judgment of the investigator, places the subject at increased risk for adverse effects
4. Has serum transaminase (i.e. aspartate aminotransferase [AST] or gamma-glutamyl transpeptidase [GGT]) levels greater than 3X the upper limit of normal (ULN) for age/gender, or serum creatinine of greater than 2X ULN at Screening
5. Pregnant or breastfeeding at Screening or planning to become pregnant (self or partner) at any time during the study
6. 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
7. 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
8. 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 aceneuramic acid 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).

DURATION OF TREATMENT:

The total treatment duration will be 48 weeks; all eligible subjects will receive 6 g/day Ace-ER. Subjects who complete the study will be eligible to participate in the extensionstudy, UX001-CL302.

CRITERIA FOR EVALUATION:

Clinical Safety Variables:

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

- Concomitant medications
- Physical examination results
- Vital signs
- Clinical laboratory results
- Interval history
- The C-SSRS

Clinical Efficacy Variables:

Efficacy will be evaluated by changes in upper and lower extremity muscle strength, physical functioning, health related quality of life outcome measures, and biomarkers. 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.

- GNEM Functional Activities Scale (GNEM-FAS) – Expanded Version: Physical functioning will be assessed using a disease-specific, clinician-reported outcome measure. Scores on the mobility, self-care and upper extremity domains of the GNEM-FAS Expanded Version will be analyzed separately
- 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. An Upper Extremity Strength Composite Score (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. Lower extremity strength will be calculated as the average of the right and left values (measured in kg).

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
- PGI-S (Patient global Impression of Severity)/PGI-C (Patient Global Impression of Change)
- Biomarkers: 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

Drug Concentration Measurements: The change in aceneuramic acid levels will be analyzed the same as for the primary endpoint.

- Serum Free SA: The change in free SA level will be analyzed to assess the drug concentration in the bloodstream resulting from treatment

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

STATISTICAL METHODS:

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. No study drug related SAE has been observed in previous clinical studies with Ace-ER. However, if it is assumed that the true rate of study drug related SAEs is 10% in this advanced patient population, there is at least 98% probability to observe one or more SAEs with N=45 subjects. Subjects who withdraw or are removed from the study after receiving study drug may be replaced on a case-by-case basis, at the discretion of Ultragenyx. This study is not powered to assess statistically significant changes from baseline in the efficacy endpoints.

Analyses Sets:

Full Analysis Set: 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.

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 subjects with evaluable free serum SA levels.

Safety Analyses:

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. 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.

Efficacy Analyses:

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). Dynamometry tests will be administered at the Screening visit to introduce subjects to performance testing to minimize training effects and will not be used for statistical analysis.

Efficacy analyses will be based on the Full Analysis Set. Generalized estimating equation (GEE) analysis will be performed with respect to the changes from baseline for all endpoints measured over time. 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.
The final analyses will be conducted at Week 48.

Table 2.1: Schedule of Events

Assessments and Events [a]	Screening [b] Day -28 to -4	Baseline [c]	Week 12 Visit (± 5 days)	Week 24 Visit (± 5 days)	Week 36 Visit (± 5 days)	Week 48 Visit (± 5 days) Or Early Termination Visit [d]	Safety Follow-up [r] (TC)
Informed Consent	X						
Inclusion/Exclusion Criteria	X	X					
Demographics	X	X					
GNEM-Specific Medical History [e]	X	X					
SAFETY ASSESSMENTS							
General Medical History, Height [f] and Weight	X						
Prior and Concomitant Medications and Therapies	X	X	X	X	X	X	X
Interval History [g]		X	X	X	X	X	
Physical Examination [h]	X	X	X	X	X	X	
Vital Signs	X	X	X	X	X	X	
Hematology, Chemistry Panel and Urinalysis [i]	X	X	X	X	X	X	
Pregnancy Test [j]	X	X	X	X	X	X	
The Columbia Suicide Severity Rating Scale	X	X	X	X	X	X	
Adverse Events	X	X	X	X	X	X	X
Urine for ManNac Testing [k]	X	X	X	X	X	X	
Biomarkers: CK, Serum SA, and Biomarkers of Sialylation and other Biomarkers [l]		X	X	X	X	X	

Assessments and Events [a]	Screening [b] Day -28 to -4	Baseline [c]	Week 12 Visit (± 5 days)	Week 24 Visit (± 5 days)	Week 36 Visit (± 5 days)	Week 48 Visit (± 5 days) Or Early Termination Visit [d]	Safety Follow-up [r] (TC)
CLINICAL ASSESSMENTS [m]							
Muscle Strength Testing by Hand-Held Dynamometry (HHD) [n]	X	X	X	X	X	X	
PATIENT-REPORTED OUTCOMES							
GNEM Functional Activities Scale (GNEM-FAS) – Expanded Version	X	X	X	X	X	X	
Medical Outcomes Survey – 36 item (SF-36) [o]		X	X	X	X	X	
PGI-S and PGI-C [p]		X	X	X	X	X	
Dispense Drug [q]		X	X	X	X		
Treatment Compliance		X	X	X	X	X	

[a] Study assessments for a subject should be performed in a consistent order at each visit. Refer to the Clinical Evaluator Manual for additional details on specific assessments and the suggested order of administration.
[b] Potential subjects can be screened up to 28 days before the Baseline Visit.
[c] Baseline Visit should be at least 4 days after and within 28 days of Screening visit. Study drug will be dispensed only after all eligibility requirements are confirmed and study procedures at the Baseline Visit have been performed.
[d] 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 (TC) within 4 weeks of discontinuation from study, where appropriate information will be collected by the clinical site.
[e] GNEM-specific medical history will include a detailed review of diagnostic and family history, as well as presenting symptoms and progression over time, and the use of assistive devices, drugs and therapies to manage the disease.
[f] 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
[g] Interval history will include any signs, symptoms, or events experienced by the subject since the prior study visit. 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.

[h] Complete physical examination including neurological examination conducted at Baseline and Week 48 (or Early Termination, if applicable) study visits. Brief physical examination at all other study visits.

[i] If urinalysis detects protein, leukocyte esterase, blood, or nitrite, urine microscopic examination will be conducted.

[j] Pregnancy test by urine dipstick (local lab) is acceptable; a serum pregnancy test should be performed in the event of a positive or equivocal urine pregnancy test result.

[k] An aliquot from the urine sample provided for the standard safety urinalysis testing will be used to test for the presence of ManNAc.

[l] 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.

[m] The muscle strength (HHD) assessment will be administered to all subjects. The number of clinical assessments performed at each visit will be determined by the subject's extent of disease involvement. The physical therapist conducting the testing will choose the appropriate number and type of assessments guided by their clinical judgment, study training, and Clinical Evaluator Manual.

[n] Lower extremity muscle strength for knee extensors muscle group only.

[o] The SF-36 will only be completed for subjects when a validated version is available in the subject's native language.

[p] PGI-S (Patient global Impression of Severity) and PGI-C (Patient Global Impression of Change): PGI-S is to be administered only at baseline. PGI-C to be administered at all subsequent visits, including Early Termination.

[q] Study drug will be dispensed only after all eligibility requirements are confirmed and study procedures at the Baseline Visit have been performed

[r] This Safety Follow-up TC is to be completed only for subjects who complete the study and choose not to enroll in the extension study, UX001-CL302, or who discontinue the study early. This call is not required for subjects who are eligible and choose to take part in Study UX001-CL302. The site personnel should initiate the Safety Follow-up TC 30 (+5) days after a subject's last dose of study drug for subjects who complete the 48-week Treatment Period or 30 (+5) days after the ET Visit or ET TC for subjects who discontinue the study early. Information on any ongoing or new AEs, SAEs, and concomitant medications will be collected. Appropriate follow-up should continue until all safety concerns, in the Investigator's opinion, are resolved.

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4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviations

6MWT	Six Minute Walk Test
Ace-ER	Aceneuramic Acid Extended Release
AE	adverse event
AFO	ankle foot orthosis/orthoses
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
cGMP	Current Good Manufacturing Practices
CK	creatine kinase
CRC	child-resistant caps
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
GGT	gamma-glutamyl transpeptidase
GNE	glucosamine (UDP-N-acetyl)-2-epimerase
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
HDPE	high-density polyethylene
HIBM	hereditary inclusion body myopathy
HIPAA	Health Insurance Portability and Accountability Act
HRQoL	Health-related Quality of Life
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)
IRB	Institutional Review Board
IVIG	intravenous immune globulin
IWRS	interactive web-based response system
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	Pharmacodynamics
PGI-S	Patient Global Impression of Severity
PGI-C	Patient Global Impression of Change
PK	pharmacokinetic(s)
PRO	patient reported outcomes
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
SA-ER	Sialic Acid-Extended Release
SA-IR	Sialic Acid Immediate Release
SAP	Statistical Analysis Plan
SF-36	Short Form Health Survey - 36
SOC	System Organ Class

SUSAR	suspected unexpected serious adverse reactions
TC	telephone call
TEAE	treatment-emergent adverse event
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 or placebo 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

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). GNEM is a rare and severely debilitating disease of adult onset myopathy and progressive muscle weakness. GNEM is an autosomal recessive disorder caused by a mutation in the GNE gene, which encodes an enzyme critical to the biosynthesis of sialic acid (SA). GNEM is typically characterized clinically by distal muscle weakness and the first symptom for most patients is unilateral or bilateral foot drop. Subsequently, impairment of both the lower and upper extremities proceeds proximally with relative sparing of the quadriceps. This impairment ultimately leads to significant compromise of upper and lower extremity function. Currently there are no approved treatments for the disease and patients eventually become wheelchair-bound as well as reliant on others for care within 10-20 years of initial diagnosis (Nonaka et al. 2005).

SA is an essential, naturally occurring amino sugar found in humans and most organisms. Defects in the SA biosynthetic pathway cause GNEM and 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. This rationale is supported by results of Murine GNE knock-out/knock-in models that demonstrated that mice with low SA levels have a phenotype resembling human GNE myopathy with impaired muscle strength and that replacement therapy with SA or its derivatives improves muscle function and histopathology associated with the disease (Yonekawa et al. 2014), (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. These results form the scientific basis for the use of SA as a replacement therapy in GNEM patients.

The product under investigation is a substrate replacement of sialic acid (SA) administered in extended release; aceneuramic acid extended release (previously known as sialic acid – extended release (SA-ER)) tablets. The sponsor has developed aceneuramic acid extended release (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 to increase free sialic acid levels in serum, thus driving uptake into muscle cells. This should restore sialylation of muscle tissues resulting in improved biochemical functions and stabilization of muscle strength and function.

The Ace-ER (previously known as SA-ER) formulation was evaluated in an initial Phase 1 study to establish the safety and pharmacokinetic (PK) profile of a single dose (fed and fasted) and 7 days of repeat dosing in 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 showed clinically meaningful, objective improvement in UE muscle strength and was supported by measurements of functional outcome on the GNEM-FAS at the higher 6 g/day Ace-ER dose level. The drug had acceptable safety profile at all doses and no SAEs were reported.

After 48 weeks of treatment, subjects from the Phase 2 randomized study entered into an open-label extension study. The open-label extension was designed in several parts to provide additional long-term safety and clinical efficacy at 6g/day dose level for continuing subjects (Part I), and evaluate the safety and efficacy of SA replacement at the 12 g/day dose level via co-administration of Ace-ER tablets with Sialic Acid immediate-release (SA-IR) capsule formulation of (Part II). (Refer to the Investigator's Brochure (IB) for additional details on SA-IR.). Most muscles tested remained stable over the course of therapy. There was an increase in AEs related to gastrointestinal (GI) tolerability at the higher 12 g/day dose and no drug related SAEs were reported. There was no additional benefit beyond the 6 g/day dose. Based on the totality of the data the 6 g/day dose demonstrated the optimal benefit to risk profile and is being further evaluated in an ongoing Phase 3 study.

The Phase 3 study is a randomized, double-blind, placebo-controlled 48-week study to evaluate efficacy and safety of Ace-ER (6 g/day) in patients with GNEM. The study will also evaluate outcome measures to determine the effect of muscle function on subject's quality of life.

In addition to interventional studies, Ultragenyx is 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 aceneuramic acid clinical development program to collect data on disease characteristics and progression.

This Phase 2 open-label study is designed to primarily evaluate the safety of 6 g/day Ace-ER tablets in GNEM patients who have severe ambulatory impairment. Efficacy will also be assessed as a secondary objective to ensure that the full spectrum of patients with GNEM is evaluated across the development program.

5.1 Overview of GNE Myopathy

GNEM was first described in the Japanese population (Nonaka et al. 1981), and in a group of Iranian Jews in Israel (Argov et al. 1984). The patients showed progressive muscle weakness and atrophy, and rimmed vacuoles on biopsy. The genetic basis of GNEM as a mutation in GNE was determined in 2001 (Eisenberg et al. 2001). Since then, patients of Italian, Japanese, Thai, Indian, American and African origin have been identified, clearly making it a

worldwide disorder (Huizing et al. 2009). GNEM is a rare disease; the incidence is low and an estimated prevalence of 1/1,000,000 (higher prevalence is seen in Middle Eastern Jews and Japanese) (Nishino et al. 2015). An estimated 220 total cases worldwide have been reported in the scientific literature (Jay et al. 2009). The Iranian Jewish population has a substantially higher incidence at approximately 1 per 1500 births (Jay et al. 2009).

Patients with GNEM have a genetic defect in the first step of the biosynthetic pathway for SA caused by mutations in the *GNE* gene coding for the bifunctional enzyme glucosamine (UDP-N-acetyl)-2-epimerase/N-acetylmannosamine kinase (GNE/MNK) (Eisenberg et al. 2001); (Jay et al. 2009). The enzyme is the rate-controlled and regulated first step in the biosynthesis of SA required for the glycosylation of proteins and lipids. Studies in tissues and mouse models have shown that the deficiency of SA production is a key factor in the disease state, though the exact pathophysiologic effect of decreased sialylation on proteins or lipids is still debated.

The clinical course in GNEM patients typically includes an onset usually after age 20 (mean 26 years, range 15–40 years) though patients can be symptomatic earlier (Nalini et al. 2010); (Nonaka et al. 2005); (Sadeh et al. 1993); (Sunohara et al. 1989). Patients often have foot drop due to tibialis anterior weakness as a first sign and general weakness is more pronounced distally which then progresses proximally. Both weakness and atrophy are noted in muscles with fatty and fibrous tissue replacement as the disease advances. In many patients, there is a relative sparing of the quadriceps for unknown reasons. The forearm flexors and axial musculature may become more involved over time. The rate of progression is gradual and variable between patients over a 10–20 year period (mean of 12 years) (Nonaka et al. 2005) leading to a wheelchair-bound state and reliance on others for care. The ocular, pharyngeal and respiratory muscles are relatively spared clinically though they may show some abnormal pathology in some patients (Argov et al. 1984). Disease progression is not rapid compared with some myopathies but ultimately the level of function reached is severely compromised.

Other clinical or physiological evaluations of these patients show a variable number of abnormalities all consistent with the myopathic pathologic process. Unlike other myopathies, creatine kinase (CK) activities are mildly elevated or in normal range (22/58 patients reported by 3 publications had 2x or higher elevations; (Sadeh et al. 1993); (Mizusawa et al. 1987b); (Sunohara et al. 1989). The mouse model of HIBM exhibits elevated CK levels that improve on treatment (Malicdan et al. 2009). The decline in muscle bulk and function is substantial but the time course of decline may be sufficiently slow as to not cause acute CK elevations as observed in other disorders like Duchenne Muscular Dystrophy. Imaging studies of the muscle by computed tomography (Sadeh et al. 1993), (Mizusawa et al. 1987a) or magnetic resonance imaging (Huizing et al. 2009) show substantial and diffuse abnormalities to muscle structure with significant fat infiltration in affected muscles but the quadriceps have a more normal appearance. Many muscles have limited muscle tissue left, which could impact the potential for optimal treatment and substantial disease reversal in advanced patients.

Currently there are no approved treatments for GNEM; existing treatment methods are supportive to manage function but do not treat the underlying disease. Treatment options may include physical and occupational therapy to improve muscle strength and, when necessary, the use of various assistive devices including braces (e.g. ankle-foot orthoses [AFOs]) or wheelchairs.

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 primarily 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). 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). In addition, 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). Nonclinical studies have been conducted in HIBM mice and multiple species of normal animals. Two clinical studies and an extension study have been conducted to characterize the PK, tolerability, safety and efficacy of SA replacement in GNEM patients.

A brief overview of existing information on Ace-ER is provided below; a comprehensive review of available data is contained in the 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.

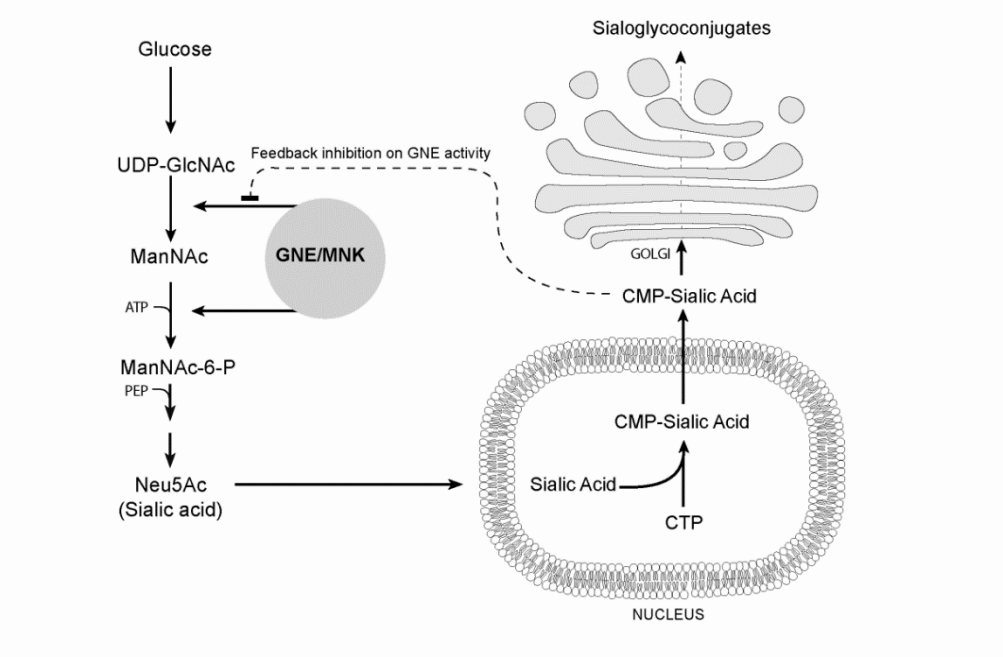
Ace-ER 500 mg tablets are white to off-white, film-coated, extended-release, oval tablets, which may be debossed with the code U-1 and are designed for oral administration. The

tablet formulation contains approximately 41.6% active pharmaceutical ingredient in a mixed polymer matrix developed for extended release of aceneuramic acid. Tablets are manufactured by a formulation process using wet aqueous granulation; the blend is then dried and compressed into tablet cores. Ace-ER 500 mg tablets are 1200 mg in total weight and packaged in 500 cc white high-density polyethylene (HDPE) bottles with screw-top polypropylene child-resistant caps (CRC) with heat-activated induction seal. Each HDPE bottle is filled with 168 tablets and contains a 3.5 gram silica gel desiccant pouch along with polyester coil.

5.2.1.1 Mechanism of Action in GNE Myopathy

GNE/MNK is an enzyme which 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). 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 SA 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} mole/L. 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 studies with SA were conducted in rats following intravenous administration of a 20 mg/kg [^{14}C]-Neu5Ac. SA was quickly excreted primarily through the urine (92.4% of radioactivity). 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.

Chronic toxicology studies in rats and dogs: In an oral 26-week rat study, there were no SA 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 this study was 2000 mg/kg/day, which is equivalent to approximately a 17 g daily human dose, providing a safety margin of approximately 3–fold over the proposed dose (6 g/day) in this clinical study. 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 this study was 2000 mg/kg/day which is equivalent to a 60 g daily human dose, thereby providing a safety margin of approximately 10–fold over the proposed dose (6 g/day) in this clinical study.

Reproductive and developmental toxicology studies in rats and rabbits: To date, reproductive and developmental 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, or treatment-related effects on pregnant females or embryo-fetal development parameters in rats and rabbits.

5.2.3 Previous Clinical Studies

Key results from studies to support the use of aceneuramic acid (also known as Sialic Acid) in treating GNEM are summarized below; additional details may be found in the IB.

Phase 1 Pharmacokinetic and Safety Study (UX001-CL101): A Phase 1 study to evaluate the safety and PK of single and repeat doses of Ace-ER tablets was conducted in GNEM

subjects. Twenty-seven (27) subjects were assigned to treatment; 26 were dosed with Ace-ER and completed dosing. Subjects received Ace-ER tablets orally at one of five dose levels (650 – 6000 mg) in the single dose phase (fasting and fed), and one of four dose levels in the repeat dose phase (1950 – 6000 mg/day divided into three equal doses).

PK analysis showed acceptable absorption of the product with SA exposure that covered about 8-16 hours. Repeat dosing for 7 days with Ace-ER showed that trough levels could be maintained above the pre-dose baseline level, as expected for a sustained release formulation.

Ace-ER was well tolerated in this group of GNEM subjects based on the AE profile, the absence of SAEs, and the lack of treatment emergent changes in any parameter (AEs, physical examinations, vital signs and clinical laboratory evaluations). The AE profile was unremarkable; the most common treatment-emergent adverse event (TEAE) reported was headache. However, there was no dose-dependent pattern for any drug-related or unrelated event.

Phase 2 Pharmacokinetic, Pharmacodynamic and Safety Study (UX001-CL201):
A Phase 2 randomized, double-blind, placebo-controlled, parallel group study was conducted to evaluate the efficacy and safety of two doses and PD of Ace-ER tablets in 47 GNEM patients (Argov et al. 2014). Subjects were randomized to receive placebo or 3 g/day or 6 g/day Ace-ER. After 24 weeks, placebo subjects crossed over (blinded) to either 3 g/day or 6 g/day Ace-ER for an additional 24 weeks. Assessments included drug concentration measurements, upper extremity composite (UEC) and lower extremity composite (LEC) muscle strength scores, other clinical endpoints, patient reported outcomes, and safety.

At Week 24, the UEC score showed a statistically significant difference in the 6 g/day group compared with placebo (+2.33 kg; p=0.040). At Week 48, a statistically significant difference between the combined 6 g/day group and the combined 3 g/day group was observed (+3.46 kg; p=0.0031). Subjects with less advanced disease (able to walk more than 200 meters at screening in the six-minute walk test, 6MWT), a predefined subset that comprised approximately 70% of total enrollment, showed a more pronounced difference at 48 weeks (+4.69 kg; 9.7% relative difference from baseline; p=0.0005).

A similar pattern of response was observed in the LEC, but was not statistically significant between the dose groups. None of the treatment groups showed a significant decline in function. There was no significant difference (increase or decline) in the 6MWT.

The GNE Myopathy Functional Activities Scale (GNEM-FAS) did not show differences at Week 24; After 48 weeks, the combined 6g/day treatment group had significantly greater LS mean scores than the combined 3 g/day group for the total score (p=0.086), mobility domain subscore (p=0.087), and upper extremity scores (p=0.096) when analyzed by the pre-specified, primary ANCOVA analysis. Changes in total, mobility, and upper extremity scores were also significant in the combined 6 g/day vs 3 g/day groups when analyzed in a post-hoc analysis.

Ace-ER appeared to be well tolerated with no SAEs reported in either dose group and no dose-dependent TEAEs identified. Common TEAEs included GI events (diarrhea, flatulence, abdominal pain, and dyspepsia), headache, arthralgia, back pain, fatigue, influenza-like illness, musculoskeletal pain, myalgia, nasal congestion and nasopharyngitis. Most AEs were mild to moderate in severity.

Phase 2 Efficacy and Safety Extension Study (UX001-CL202): An open-label Phase 2 extension study is ongoing to assess the long-term safety and efficacy of 6 g/day Ace-ER and 12 g/day SA-ER/SA-IR in GNEM patients. In Part I of the study, 46 subjects were enrolled following successful completion of the UX001-CL201 study. Throughout the Part I Treatment Period of the study, all subjects continued on 6 g/day Ace-ER tablets administered three times a day (TID). In Part II of the study, all subjects crossed over to the 12 g/day SA-ER/SA-IR dosing regimen. An additional 13 treatment naïve GNEM subjects were also enrolled into Part II of the study to receive 12 g/day. In Part III of the study, some subjects had their dose reduced from 12 g/day to 6 g/day. The treatment-naïve group and a subset of rollover subjects who showed potential clinical benefit at 12 g/day had the option to remain on the 12 g/day dose.

Evaluations include safety, changes in clinical endpoints such as muscle strength, mobility, and function, and changes in exploratory serum biomarkers. Data from assessment at the end of Part II (Month 12 Visit) suggest that the 12 g/day dose does not confer additional benefit than the 6 g/day dose in muscle strength or clinical endpoints. At this cut-off, after 2.5 years of SA treatment (combined duration of UX001-CL201 and 12 month cut-off of UX001-CL202) three of the four muscle group that comprise UE strength and four of the five muscle groups that comprise LE strength remained stable in the combined 0/6 g/day and 6/6 g/day group as evidenced by an increase in LS mean strength or a reduction in LS mean strength of < 1.0 kg from the UX001-CL201 Baseline Visit.

The 12 g/day dose of SA was generally well tolerated but AEs related to GI tolerability were increased. AEs were generally mild to moderate in severity and similar to those observed in previous studies.

Phase 3 Efficacy and Safety Study (UX001-CL301): A Phase 3, randomized, double-blind, placebo-controlled study to evaluate efficacy and safety of 6 g/day Ace-ER in GNEM patients is currently ongoing and enrolling patients. Currently there are no data available from this study.

5.2.4 Summary of Overall Risks and Potential Benefits

Since SA is an endogenous monosaccharide with native pathways for degradative metabolism and rapid renal clearance, and there is no evidence or expectation of a significant safety issue with SA replacement therapy. Data from nonclinical and clinical studies to date suggest Ace-ER administered alone or with SA-IR does not pose any significant safety risks that can be identified at this time. Toxicology or adverse pharmacology findings were not

observed in SA-treated animals; at very high doses, osmotic diarrhea may be observed in treated dogs.

In the 48-week Phase 2 study in 47 GNEM subjects, there were no deaths or drug related SAEs. The majority of subjects had TEAEs that were graded as mild to moderate severity. A single subject in the 3 g/day Ace-ER group discontinued due to an AE of abnormal liver enzymes; the subject was subsequently identified as having a history of elevated liver function test results. The only AE experienced by a greater proportion of Ace-ER treated subjects was abnormal liver function tests (5 subjects vs. 0 in the placebo group). It is likely alanine aminotransferase (ALT) elevations resulted from skeletal muscle disease rather than from liver damage, since gamma-glutamyl transpeptidase (GGT) was generally normal and serum CK was also elevated in these subjects. The time course of abnormality and lack of dose response suggest that these results are not study drug related. Sporadic abnormal levels of aspartate aminotransferase (AST) and ALT were also reported throughout the study, irrespective of time point or treatment group.

The most common treatment-related TEAEs were GI events (diarrhea, flatulence, abdominal pain, and dyspepsia), headache, and fatigue. The patterns of AEs were similar in the placebo-controlled phase of the study (the first 24 weeks) and for all 48 weeks. No correlation was observed between the GI events and free SA serum levels suggesting the frequency of GI events does not appear to be dose dependent. No subjects from the Placebo group reported diarrhea or abdominal pain, or had abnormal liver function tests after crossing over to Ace-ER treatment in the continuation phase of the study.

Safety results in the ongoing Phase 2 study (UX001-CL202) indicate the most common TEAE reported by subjects receiving a higher dose of 12 g/day SA-ER/SA-IR involve GI disorders, including diarrhea, flatulence, dyspepsia, and abdominal pain.

In clinical studies conducted to date, 6 g/day Ace-ER provided a sustained exposure, a clinical efficacy signal, and acceptable safety profile. Overall the risk-benefit ratio appears to be favorable based on the excellent safety record to date, and the potential benefit observed in nonclinical and clinical studies.

5.3 Study Rationale

GNEM (or HIBM), is a rare, severely debilitating disease of adult onset myopathy and progressive muscle weakness 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 reduced SA and resulting reduction of 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 aceneuramic acid extended release [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 better preserved muscle strength compared with placebo or the lower 3 g/day Ace-ER dose, and the difference in

upper extremity muscle strength (UEC score) between the highest and lowest exposure group was statistically significant. This finding was supported by measurements of functional outcome on the GNE Myopathy Functional Activities Scale (GNEM-FAS). Based on these results, a Phase 3 study is being conducted to further evaluate and confirm the efficacy of Ace-ER 6 g/day to preserve upper extremity muscle strength and function (UX001-CL301). The primary objective of this Phase 2 study will be to evaluate the safety of open-label 6 g/day Ace-ER in GNEM subjects with severe ambulatory impairment; efficacy will also be assessed as a secondary objective to ensure that the full spectrum of patients with GNEM are evaluated.

For the purposes of this study, a subject with severe ambulatory impairment is defined as:

- Unable to rise from a seated position to standing without help from another person, assistive device(s), stationary object, or other support

  AND

- Unable to walk without the assistance of another person OR if able to walk (use of assistive device(s) permitted), requires at least 2 minutes to walk 40 meters (one full lap of the 6MWT course)

  AND

- Use of wheelchair or scooter for activities outside of the home or unable to leave the home independently

6 STUDY OBJECTIVES

Primary Objective: Evaluate the safety of Ace-ER in GNEM subjects with severe ambulatory impairment

Secondary Objectives: Evaluate the efficacy of 6 g/day of Ace-ER in GNEM subjects with severe ambulatory impairment

Exploratory Objectives: Evaluate the effect of 6g/day Ace-ER on HRQoL, patient reported outcomes (PRO), and biomarkers of sialyation

6.1 Study Endpoints

6.1.1 Primary Endpoint

The primary endpoint of the study is the incidence and frequency of AEs and SAEs assessed as related to Ace-ER over the duration of the study.

6.1.2 Secondary Endpoints

The secondary safety endpoints of the study are:

- Clinically significant changes from baseline to scheduled time points in concomitant medications, physical examination results, vital signs, clinical laboratory results and interval history during the course of the study

The secondary efficacy endpoints of the study are:

- Change in GNEM-FAS Expanded Version total score and mobility, upper extremity and self-care domain scores from baseline over the duration of the study
- Change in upper extremity strength in the following muscle groups: grip, key pinch, shoulder abductors and wrist extensors as measured by dynamometry over the duration of study
- Change in lower extremity muscle strength in the knee extensors as measured by dynamometry over the duration of the study

6.1.3 Exploratory Endpoints

The exploratory endpoints of the study include HRQoL, patient reported outcomes and biomarker analyses.

- Change in health-related quality of life as assessed by using Short Form Health Survey - 36 (SF-36) over the duration of the study
- Change in symptom severity as measured by Patient Global Impression of Severity (PGI-S) and Patient Global Impression of Change (PGI-C) over the duration of the study
- Changes in serum CK as a marker of muscle injury over the duration of the study
- Changes in biomarkers of sialylation

7 INVESTIGATIONAL PLAN

7.1 Overall Study Design and Plan

This is an open-label, multicenter study to assess safety of Ace-ER in GNEM patients with severe ambulatory impairment. Efficacy will be assessed as a secondary objective. Approximately 45 subjects will be enrolled in the study and receive 6 g/day of Ace-ER for 48 weeks.

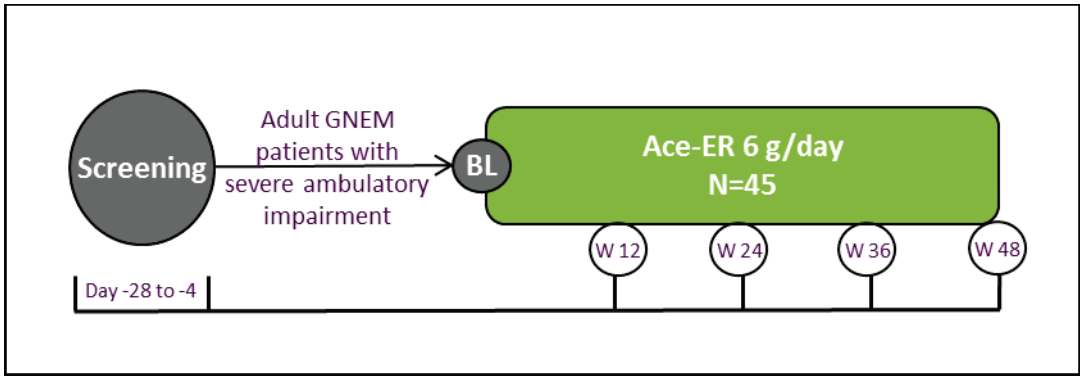
Subjects will take 4 tablets (500 mg each for 2 g per dose) orally 3 times per day (TID). The dose should be taken with food (i.e. within 30 minutes after a meal or snack). Treatment will be administered for a total of 48 weeks. Study visits will occur every 12 weeks during the Treatment Period during which the scheduled assessments will be administered 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, and concomitant medications.

Information on biomarkers will be collected to assess their value in predicting clinical severity and disease progression, as well as the ability to determine the long-term impact of disease-targeted treatments and therapies for GNEM.

Efficacy will be evaluated by dynamometry as a measure of muscle strength and patient-reported outcome measures as measures of disability and quality of life. 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 2 study is designed to evaluate the long-term safety of 6 g/day Ace-ER in GNEM patients with severe ambulatory impairment. Efficacy will be measured as a secondary

objective. In addition, information on biomarkers will be collected to assess their value in predicting clinical severity and disease progression.

The study will be conducted as an open-label study as its primary objective is to assess the safety in GNEM patients with severe ambulatory impairment. There will be no control arm in the study.

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 and interval history will also be part of the safety evaluation.

The study population comprises adult GNEM patients with severe ambulatory impairment, since the onset of disease usually occurs after age 20, and seeks to evaluate the safety of Ace-ER in this patient population. Enrolled subjects will have a confirmed diagnosis of GNEM; however the population is inherently limited to only those subjects with severe ambulatory impairment. These subjects have advanced disease and while not all of them are entirely wheelchair bound, they do require assistance from another person or assistive device to stand from a seated position and for performing activities outside the home. Please see Inclusion Criteria Section 7.3.1 for the definition on severe ambulatory impairment.

The 48-week treatment design is intended to allow for a sufficient duration to observe any potential safety impact of the 6g/day dose level in this severely compromised GNE myopathy patient group. In addition, it will allow for a minimal collection of efficacy data to determine the clinical effect of aceneuramic acid in these patients.

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.

7.3.1 Inclusion Criteria

1. Male or female, aged ≥ 18 years old
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. Have a documented diagnosis of GNEM, HIBM, DMRV, or Nonaka disease due to previously demonstrated mutations in the gene encoding the GNE/MNK enzyme (genotyping will not be conducted in this study)
4. Should meet the criteria for severe ambulatory impairment defined below:

- Unable to rise from a seated position to standing without help from another person, assistive device(s), stationary object, or other support

  AND

- Unable to walk without the assistance of another person OR if able to walk (use of assistive device(s) permitted), requires at least 2 minutes to walk 40 meters (one full lap of the 6MWT course)

  AND

- Use of wheelchair or scooter for activities outside of the home or unable to leave the home independently

5. Willing and able to comply with all study procedures
6. 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 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
7. 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), SA, 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. Prior participation in a clinical trial involving treatment with Ace-ER/placebo and/or SA-IR in the past year

3. Has had any hypersensitivity to aceneuramic acid or its excipients that, in the judgment of the investigator, places the subject at increased risk for adverse effects
4. Has serum transaminase (i.e. aspartate aminotransferase [AST] or gamma-glutamyl transpeptidase [GGT]) levels greater than 3X the upper limit of normal (ULN) for age/gender, or serum creatinine of greater than 2X ULN at Screening
5. Pregnant or breastfeeding at Screening or planning to become pregnant (self or partner) at any time during the study
6. 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
7. 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
8. 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 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 by the time of the Safety Follow-up TC or, if applicable, until the date the subject receives their first dose of study drug in the extension study, UX001-CL302, whichever occurs sooner , 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 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 by the Medical Monitor as to whether the subject will continue on the study.

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 45 subjects will be enrolled in to the study and treated with Ace-ER tablets; 6 g/day divided TID.

7.4.1 Investigational Product

Each Ace-ER tablet contains 500 mg of aceneuramic acid in an extended release formulation for a total weight of 1200 mg/tablet. The 6000 mg (6 g) total daily 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 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 less efficacious, and that a higher dose of 12 g/day did not result in a significant improvement over 6 g/day. These data

were derived from a randomized, placebo-controlled Phase 2 study and a corresponding extension study.

The Phase 2, double-blind, randomized, placebo-controlled study (UX001-CL201) evaluated treatment with Ace-ER at two dose levels (3 g/day and 6 g/day). The study was placebo controlled for the first 24 weeks and then all subjects received Ace-ER at one of the two doses (blinded) for the next 24 weeks. In this study, the group of patients treated with higher dose of 6 g/day (placebo or 6 g/day for first 24 weeks followed by 6 g/day for next 24 weeks) stabilized upper extremity muscle strength compared with patients treated with lower dose of 3 g/day (placebo or 3 g/day dose for first 24 weeks then 3 g/day for the next 24 weeks). This finding was also supported by measurements of functional outcome on the GNEM-FAS indicating the difference in muscle strength was clinically meaningful to subjects.

A higher 12 g/day dose administered as 1.5 g Ace-ER and 1.5 g SA-IR orally four times daily was evaluated in Part II of the Phase 2 extension study (UX001-CL202) in existing subjects who transitioned from 6 g/day to 12 g/day, and in 13 treatment-naïve subjects who initiated treatment at 12 g/day. No additional efficacy benefit was conveyed by the 12 g/day dose over the 6 g/day dose. The safety of the 12 g/day dose appeared generally similar to 6 g/day but with a notable increase in GI symptoms, including flatulence.

Given these biochemical and clinical results, the 6 g/day Ace-ER dose has been selected for further study as the dose with a treatment effect that will provide the best opportunity for efficacy in all subjects with a good safety profile.

Study Duration:

Individual subject participation in this study will be a maximum of approximately 56 weeks, including up to 4 weeks between Screening and Baseline, 48 weeks of treatment, and a Safety Follow-up Period of approximately 4 weeks. Subjects who complete the study may be eligible to participate in the open-label extension study, UX001-CL302.

All subjects will receive Ace-ER 6 g/day during the 48-week Treatment Period. The 48-week treatment duration is intended for adequate collection of safety data on the Ace-ER tablets and to provide insight on sustained clinical effects and improvements in adult GNEM patients with severe ambulatory impairment.

7.4.3 Method of Assigning Subjects to Treatment Groups

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

7.4.4 Prior and Concomitant Therapy

7.4.4.1 Prohibited Medications

Patients may not be enrolled if they have participated in another aceneuramic acid study involving treatment with Ace-ER/placebo and/or SA-IR in the past year, used any investigational product 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 or related metabolites; IVIG; or anything that can be metabolized to produce SA in the body is prohibited during the 60 days prior to Screening and throughout the study. If ManNAc, SA 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 urine for the presence of ManNAc to detect noncompliance with this essential requirement.

7.4.4.2 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, dose, route and the reason the medication was taken.

7.4.5 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. All used product packaging and containers must also be returned at in-clinic visits. Drug accountability will be assessed by site personnel and recorded. Measurements of free SA levels in the serum may also analyzed to 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-CL203, along with timing of assessments, are provided in the Schedule of Events (Table 2.1). Study assessments for a subject should be performed in a consistent order at each visit. Refer to the Clinical Evaluator Manual for additional details on specific assessments and the suggested order of administration.

7.5.1 Study Schedule

The Schedule of Events (Table 2.1) details all procedures to be completed at each visit and should serve as the primary section of the protocol regarding visit-specific study procedures.

7.5.1.1 Screening Period

Informed consent must be obtained prior to administering any Screening procedures. Screening procedures may take place across multiple days to allow enough time to complete all procedures and confirm initial subject eligibility. Screening procedures and dates should be well documented in the source documents and CRF. For recording purposes, the date of the Screening Visit is the date the patient has signed informed consent for this study.

7.5.1.2 Baseline Visit

The Baseline (Week 0) Visit should take place at least 4 days after and within 28 days of the Screening Visit. Baseline visit (Week 0) assessments must be completed prior to first dose of study drug.

7.5.1.3 Treatment Period

Subjects will return to the clinic at 12-week intervals (± 5 days) throughout the Treatment Period (Weeks 0 – 48). For subjects who discontinue prior to completing the 48-week Treatment Period, every reasonable effort should be made to perform the Early Termination Visit procedures within four weeks of discontinuation (Section 7.5.1.4).

7.5.1.4 End of Study (Week 48)/Early Termination Visit

All enrolled subjects who complete the study or discontinue early (i.e., prior to completing the 48-week Treatment Period) should complete the Week 48/Early Termination Visit.

For subjects who discontinue early, 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 (TC) within 4 weeks of discontinuation from study, where information on any ongoing or new AEs, SAEs, and concomitant medications will be collected by the clinical site.

7.5.1.5 Safety Follow-up Period

A Safety Follow-up TC should be initiated by the site personnel 30 (+5) days after a subject's last dose of study drug for subjects who complete the 48-week Treatment Period and choose not to enroll in the extension study, UX001-CL302, or 30 (+5) days after the ET Visit or TC for subjects who discontinue the study early. Information on any ongoing or new AEs, SAEs, and concomitant medications should be collected. Appropriate follow-up of ongoing AE/SAEs should continue until all safety concerns, in the Investigator's opinion, are resolved.

Subjects who have completed the Week 48 Visit of this study, meet the requirements of extension Study UX001-CL302, and choose to enroll in the extension study will not be required to complete the Safety Follow-up TC. However, note that for these subjects, AEs/SAEs should continue to be collected in the parent study until the date of their first dose of study drug in the extension study (see Section 8.5.4).

7.5.2 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, and also 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.

7.5.2.1 Medical History

A detailed medical history will be obtained at the Screening 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.

7.5.2.2 Height and Weight

Height and weight will be captured at the Screening Visit and should be measured by the trained clinician administering the performance testing. A calibrated stadiometer must be used for all height measurements. If a patient is unable to stand or has significant postural issues that interfere with the collection of a standing height, self-reported final adult height should be captured. Height should be measured in 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 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 Visit will be used for all derivations of percent predicted.

7.5.2.3 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 (except Screening).

7.5.2.4 Physical Examination

Complete physical examinations including neurological examinations will be performed at Baseline and the Week 48 study visit (or Early Termination, if applicable) and brief physical examinations at all other visits. Complete physical examinations will include assessments of general appearance; head, eyes, ears, nose, and throat; the cardiovascular, dermatologic, lymphatic, respiratory, GI, 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 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.

7.5.2.5 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.

7.5.2.6 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 are listed in Table 7.5.2.6.1. Clinical laboratory testing will be performed at every visit. Refer to the Laboratory Manual for details regarding collection and processing instructions of samples.

Table 7.5.2.6.1: Clinical Laboratory Assessments for Safety

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

If urinalysis detects protein, leukocyte esterase, blood, or nitrite, urine microscopic examination will be conducted. The microscopic examination will include white blood cells (WBCs); red blood cells (RBCs); epithelial cells: squamous, transitional, and renal tubular; casts: hyaline, WBC, RBC, waxy, and granular; crystals: calcium oxalate, uric acid, and triphosphate; yeast; bacteria; amorphous urates; and amorphous phosphates.

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.

7.5.2.6.1 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 7.5.2.6.1.1). 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 7.5.2.6.1.1: Volume of Blood to be Drawn from Each Subject

Assessment		Sample Volume (mL)	Number of Samples	Total Volume (mL)
Safety	Chemistry [1]	7.5	6	45
	Hematology	3	6	18
PK	Sialic Acid	5	5	25
Total mL through study completion				88

[1] Includes CK, an efficacy variable

7.5.2.7 Pregnancy Testing

Female subjects of childbearing potential with a positive pregnancy test at Screening will not be eligible to enroll in the study. Female subjects will have urine pregnancy tests at the Baseline visit and at 12-week intervals throughout the study (or Early Termination).

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).

7.5.2.7.1 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. The sponsor or it's designee will provide details on the reporting procedures to follow in the event of pregnancy.

7.5.2.8 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 (FDA Draft Guidance 2012). The Columbia Suicide Severity Rating Scale (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 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.

7.5.2.9 Concomitant Medications

Concomitant medications will be reviewed and recorded in the subject's CRF at each study visit, beginning at the Screening visit. Medications (investigational, prescription, over-the-counter, and herbal) and nutritional supplements taken during the 30 days prior to Screening 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 7.4.4.

7.5.2.10 Adverse Events

All AEs will be recorded from the time the subject signs the informed consent through the Safety Follow-up TC, or, if applicable, until the date the subjects receive their first dose of study drug in the extension study, UX001-CL302, whichever occurs sooner.
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.

7.5.3 Efficacy Measures

Efficacy will be evaluated by changes in physical functioning, upper and lower extremity muscle strength, HRQoL outcome measures, and biomarkers. In addition to total score, scores of mobility, self-care and upper extremity domains of the GNEM-FAS Expanded Version will be analyzed separately. 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.

7.5.3.1 Dynamometry

Dynamometry testing of multiple muscle groups will be used to measure strength. Dynamometry sessions will occur at each visit beginning with the Screening Visit. Test administration at the Screening visit is intended as practice for the evaluator and the subject and data collected will not be used for analysis. See Clinical Evaluator Manual for details on the administration procedure for dynamometry.

Formal training will be conducted with the clinicians administering dynamometry (preferably 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: shoulder abductors, wrist extensors and knee extensors. Specialized dynamometers for the measurement of gross grip and pinch strength will also be used.

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); (Peters et al. 2011). Muscle strength and percent predicted values for each muscle group tested will be analyzed (Section 7.6.4).

7.5.3.1.1 Upper Extremity Strength Composite (UEC) Score

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 change from baseline in mean UEC score will be measured and reported.

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.

7.5.3.1.2 Lower Extremity Muscle Strength

Muscle strength based on MVIC against a dynamometer will be measured bilaterally in the knee extensors muscle group for subjects who are able to be positioned properly for valid testing. Lower extremity muscle strength will be calculated as the average of the right and left values (measured in kg).

7.5.3.2 GNEM Functional Activities Scale (Expanded Version)

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 GNEM-FAS will be administered at each visit beginning with the Screening Visit to evaluate physical functioning. Test administration at the Screening visit is intended as practice for the evaluator and the subject, and data collected will not be used for analysis. 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 original GNEM-FAS was developed as a clinician-reported outcome measure (ClinRo) for ambulatory GNEM patients but has since been modified to include additional items to accommodate weaker patients. This modified version is referred to as the GNEM-FAS Expanded Version and will be used in this study.

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

The SF-36 will be completed by subjects at each visit beginning with the Baseline Visit 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 only be completed for subjects when a validated version is available in the subject's native language.

7.5.3.4 Patient Global Impression of Severity (PGI-S) and Patient Global Impression of Change (PGI-C)

The PGI-S/PGI-C is an instrument widely used in chronic pain clinical trials to indicate the patient's perception about the efficacy of treatment (Mease et al. 2011). It's a self-administered tool and improvement is rated on a 7-point categorical scale ranging from "very much better" to "very much worse." A 7-point PGI-S instrument will be administered at the Baseline visit to ascertain patient perception of disease severity before start of the study treatment. The PGI-C will be completed at all subsequent visits including Early Termination

Visit, if applicable, to ascertain the change in patient's perception of disease severity over the duration of treatment.

7.5.3.5 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 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.

7.5.4 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 (including Early Termination, if applicable) a serum sample will be collected, prior to the morning dose of study medication (pre-dose) if possible, to assess levels of free SA.

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

7.5.5 Urine Testing for ManNAc

An aliquot from the urine sample provided for the standard urinalysis testing at Screening, Baseline and each subsequent visit (including Early Termination, if applicable) will be analyzed for the presence of ManNAc to detect noncompliance with prohibited medication restrictions.

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

7.5.6 Appropriateness of Measures

The safety parameters to be evaluated in this study include standard assessments such as recording of medical history, AEs and SAEs, physical examination, vital signs, serum chemistry, and other routine clinical and laboratory procedures. In addition, symptoms of increasing muscle weakness 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).

The secondary efficacy parameters to be evaluated in this study include changes in upper and lower extremity muscle strength, changes in self-reported functional disability using a disease-specific questionnaire, and changes in self –reported health related quality of life. Based on results from Phase 2 studies and published studies (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). A disease-specific, self-reported measure designed to evaluate ability in

GNEM patients (GNEM-FAS Expanded Version) will be administered in this study to support the clinical meaningfulness of changes in muscle strength.

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).

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. No study drug related SAE have been observed in previous clinical studies with Ace-ER. However, if it is assumed that the true rate of study drug related SAEs is 10% in this advanced patient population, there is at least 98% probability to observe one or more SAEs with N=45 subjects. Subjects who withdraw or are removed from the study after receiving study drug may be replaced on a case-by-case basis, at the discretion of Ultragenyx. This study is not powered to assess statistically significant changes from baseline in the efficacy endpoints.

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 randomized 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

Baseline values for each endpoint will be defined as the last scheduled data collection visit before beginning treatment according to the Schedule of Events (Table 2.1). Dynamometry will be administered at the Screening visit to determine eligibility and introduce subjects to performance testing to minimize training effects and will not be used for analysis purposes.

Efficacy analyses will be based on the Full Analysis Set. Generalized estimating equation (GEE) analysis will be performed to assess the changes from baseline of all efficacy endpoints with repeated measurements. Baseline will be included as a covariate in the model.

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. All analyses and tabulations will be performed using SAS®. 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. The final analysis will be conducted at Week 48.

7.6.5 Analyses of Drug Concentration Measurements

The SA analysis set will be used to evaluate free serum SA levels . Changes from baseline will be analyzed using the GEE method for repeated measures analysis.

7.6.6 Safety Analyses

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

- Concomitant medications
- Physical examination results
- Vital signs
- Clinical laboratory results
- Interval history
- The C-SSRS

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. 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 IRB/Ethics Committee (EC) must be a properly constituted board or committee operating in accordance with 21 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 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 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 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 two years after the last approval of a marketing application in the US or an ICH region and until: 1) there are no pending or contemplated marketing applications in the US or an ICH region, or 2) at least two years have elapsed since the formal discontinuation of clinical development of the investigational product under study. The Investigator/institution should retain subject identifiers for at least 25 years after the completion or discontinuation of the study. 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. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an Ultragenyx agreement. 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 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 collected from the time the subject signs informed consent through the Safety Follow-up TC or, if applicable, until the date the subject receives the first dose of study drug in the extension study, UX001-CL302, whichever occurs sooner. In addition, for those subjects choosing not to enroll in Study UX001-CL302, the Investigator should report

any AE they are made aware of that occurs after the Safety Follow-up TC and that is believed to have a reasonable possibility of being associated with study drug.

AEs ongoing at the time of the Safety Follow-up TC or the date of the first dose of study drug in the extension study 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 the Safety Follow-up TC or, if applicable, until the date the subject receives the first dose of study drug in the extension study, UX001-CL302, whichever occurs sooner, 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 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 suspected unexpected serious adverse reactions (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 Ace-ER, 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 the Safety Follow-up TC or, if applicable, until the date the subject receives the first dose of study drug in the extension study, UX001-CL302, whichever occurs sooner.

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 the Safety Follow-up TC or, if applicable, until the date the subject receives the first dose of study drug in the extension study, UX001-CL302, whichever occurs sooner. 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: PPD e-mail: PPD	Hank Mansbach, MD Telephone: PPD e-mail: PPD

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

Protocol Number: UX001-CL203, Amendment 1

I have read Protocol UX001-CL203, 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.

PPD PPD

Hank Mansbach, M.D. Date
Vice President, Global Medical Affairs
Ultragenyx Pharmaceutical Inc.