

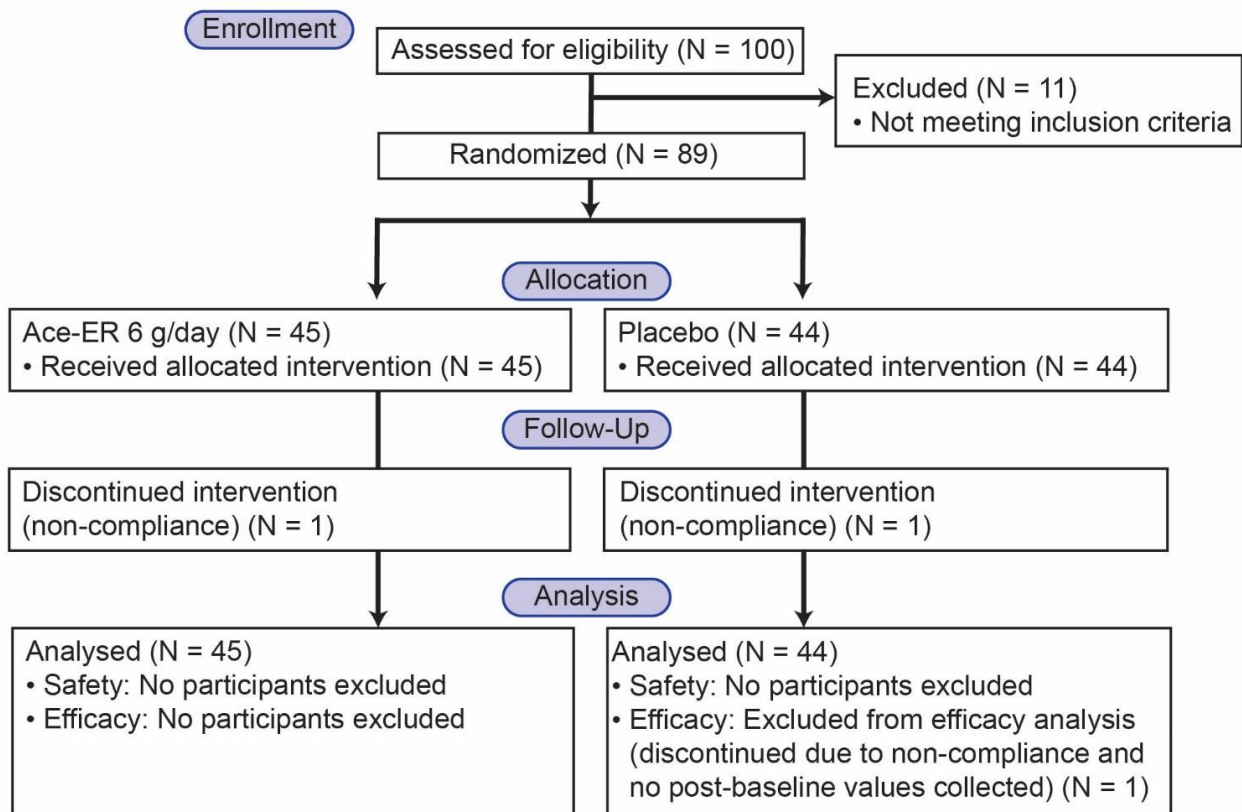
**Table e-1. Change from Baseline to Week 48 in UEC and LEC Individual Muscle Groups with Hand-Held Dynamometry**

<b>Muscle Group</b>	<b>Placebo (N=43)</b>	<b>Ace-ER 6 g/day (N=45)</b>	<b>Difference (Ace-ER-Placebo)</b>
<b>Gross Grip, kg</b>			
Baseline, mean (SD)	21.18 (14.18)	21.64 (13.40)	-
LSM (95% CI) Change from Baseline	-1.33 (-2.22, -0.45)	-1.82 (-2.57, -1.07)	-0.49 (-1.67, 0.70)
<b>Shoulder Abductors, kg</b>			
Baseline, mean (SD)	12.52 (5.58)	11.69 (4.93)	-
LSM (95% CI) Change from Baseline	-0.11 (-0.84, 0.61)	0.39 (-0.39, 1.17)	0.50 (-0.56, 1.56)
<b>Elbow Flexors, kg</b>			
Baseline, mean (SD)	12.79 (7.83)	12.82 (6.52)	-
LSM (95% CI) Change from Baseline	-1.05 (-1.77, -0.32)	-0.54 (-1.22, 0.15)	0.51 (-0.44, 1.46)
<b>Elbow Extensors, kg</b>			
Baseline, mean (SD)	9.81 (4.82)	9.84 (5.32)	-
LSM (95% CI) Change from Baseline	-0.50 (-0.96, -0.04)	-0.28 (-0.72, 0.16)	0.22 (-0.40, 0.85)
<b>Hip Abductors, kg</b>			
Baseline, mean (SD)	17.16 (8.89)	17.57 (9.20)	-
LSM (95% CI) Change from Baseline	-0.40 (-1.41, 0.60)	-0.11 (-1.02, 0.81)	0.30 (-1.07, 1.66)
<b>Hip Adductors, kg</b>			
Baseline, mean (SD)	8.46 (7.63)	7.67 (6.55)	-
LSM (95% CI) Change from Baseline	0.27 (-0.68, 1.22)	-0.03 (-0.90, 0.85)	-0.30 (-1.58, 0.99)
<b>Hip Flexors, kg</b>			
Baseline, mean (SD)	7.76 (7.84)	6.80 (6.98)	-
LSM (95% CI) Change from Baseline	-0.38 (-1.21, 0.45)	-0.36 (-1.12, 0.40)	0.02 (-1.08, 1.12)
<b>Hip Extensors, kg</b>			
Baseline, mean (SD)	13.88 (10.42)	13.90 (8.78)	-
LSM (95% CI) Change from Baseline	0.74 (-0.88, 2.36)	-0.60 (-1.91, 0.70)	-1.34 (-3.40, 0.72)
<b>Knee Flexors, kg</b>			
Baseline, mean (SD)	7.91 (8.44)	7.58 (6.45)	-
LSM (95% CI) Change from Baseline	-0.73 (-1.41, -0.06)	-0.82 (-1.21, -0.43)	-0.09 (-0.86, 0.68)

CI, confidence interval; LEC, Lower Extremity Composite; LSM, Least Squares Mean; UEC, Upper Extremity Composite

## Figure e-1. UX001-CL301 CONSORT Flow Diagram

Figure e-1. Study UX001-CL301 CONSORT Diagram





**A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Sialic Acid Extended-Release Tablets in Patients with GNE Myopathy (GNEM) or Hereditary Inclusion Body Myopathy (HIBM)**

<b>Protocol Number:</b>	<b>UX001-CL301</b>
<b>Original Protocol:</b>	<b>22 January 2015</b>
<b>Amendment 1:</b>	<b>16 March 2015</b>
<b>Amendment 2:</b>	<b>23 September 2015</b>
<b>Amendment 3 (Italy):</b>	<b>16 December 2015</b>
<b>Amendment 4:</b>	<b>25 March 2016</b>
<b>Amendment 5:</b>	<b>25 May 2017</b>

**Investigational Product:** Sialic Acid Extended-Release (SA-ER) Tablets

**Indication:** Treatment of GNE myopathy (GNEM), also known as hereditary inclusion body myopathy (HIBM), distal myopathy with rimmed vacuoles (DMRV), or Nonaka disease

**IND/EudraCT Number:** 109,334 / 2014-005432-33

**Sponsor:** Ultragenyx Pharmaceutical Inc.  
60 Leveroni Court  
Novato, CA 94949 USA

**Sponsor's Responsible Medical Officer:** [REDACTED]

**Coordinating Investigator:** [REDACTED]

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

**Confidentiality Statement:** This document and the information it contains is confidential and proprietary and is the property of Ultragenyx Pharmaceutical Inc. (Ultragenyx). Unauthorized disclosure, reproduction, transmission, or use of this document or information is strictly prohibited. By accepting this document, the recipient agrees that the information it contains will not be disclosed without written authorization from Ultragenyx, except to the extent required to satisfy Institutional Review Board /Ethics Committee procedures, to obtain written informed consent from potential subjects, or as required by law.

## CLINICAL STUDY PROTOCOL AMENDMENT SUMMARY OF CHANGES AND RATIONALE

### UX001-CL301 Amendment 5

25 May 2017

---

Protocol UX001-CL301 Amendment 4 (dated 25 March 2016) has been modified by Amendment 5 to align the order of the study objectives and identification of key secondary endpoints between the Protocol and the Statistical Analysis Plan (SAP) documents as requested by the US Food and Drug Administration. In addition, the Protocol's planned statistical analyses were updated to include multiplicity adjustment for the 3 key secondary clinical efficacy endpoints, and to include geographic region and gender as covariates for the primary clinical efficacy endpoint. Minor edits and typographical corrections were also made. Important changes to the protocol are summarized below.

1. **Study Objectives.** In Section 6, the study objectives have been modified to designate 3 secondary objectives as "key" secondary objectives. These 3 secondary objectives are To evaluate the effect of 6 g/day of SA-ER treatment of subjects with GNEM on the following:

- Lower extremity composite muscle strength score as measured by dynamometry
- Muscle strength in the knee extensors as measured by dynamometry
- Physical functioning as measured using the GNEM-FAS mobility domain score

*Rationale:* These changes to study objectives were made to ensure the consistency in the designation of objectives between the Protocol and the SAP and to clearly identify the key secondary objectives for the study that represent muscle strength and physical functioning.

2. **Secondary Efficacy Endpoints:** In Section 7.6.4.2.1 and related sections, 3 secondary clinical efficacy endpoints were designated as "key" secondary endpoints. These include the following:

- Lower extremity composite (LEC) score based on a sum of the mean bilateral strength recorded in the following muscle groups: knee flexors, hip flexors, hip extensors, hip abductors, and hip adductors
- Muscle strength in the knee extensors: bilateral total force (in kg)
- GNEM-FAS mobility domain score

Percent predicted muscle strength in the knee extensors was previously included as a secondary endpoint (in addition to total force) and is now listed separately as a tertiary endpoint.

*Rationale:* These changes were made to ensure the consistency of the Protocol and the SAP documents. Those secondary endpoints designated as "key" represent both muscle strength and physical functioning and represent key aspects of GNEM disease.

- 3. Statistical Analysis:** In Section 7.6.4.2.1, text was added to indicate that Hochberg's adjustment for multiplicity will be applied for the 3 key secondary endpoints. In addition, geographic region and gender were added as covariates for the primary efficacy analysis.

*Rationale:* These changes were made to align the Protocol with the SAP. The addition of Hochberg's multiplicity adjustment for the 3 key secondary endpoints was implemented to provide increased statistical rigor (reduced risk for type I statistical errors) with the testing of multiple hypotheses. The second change, addition of region and gender as covariates, was made to account for potential heterogeneity of the disease in different regions due to genetic variations and to account for potential differences in muscle strength between males and females.

- 4. Urinary Sialic Acid Assessment:** In Section 6 and Section 7.5.3, the language regarding urinary SA as a tertiary objective and its assessment has been modified. Urinary SA will be measured but will not be used as a determination of SA-ER absorption, excretion, and pharmacodynamics.

*Rationale:* Because formal pharmacokinetics analyses are not being performed in the study, urinary SA levels will have limited use as measures of absorption, excretion, and pharmacodynamics.

## 2 SYNOPSIS

**TITLE OF STUDY:**

A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Sialic Acid Extended-Release Tablets in Patients with GNE Myopathy (GNEM) or Hereditary Inclusion Body Myopathy (HIBM)

**PROTOCOL NUMBER:**

UX001-CL301

**STUDY SITES:**

Approximately 15 sites, globally

**PHASE OF DEVELOPMENT:**

Phase 3

**RATIONALE:**

GNEM (or HIBM), is a severe, progressive myopathy caused by a defect in the biosynthetic pathway for sialic acid (SA). Substrate replacement is a potential therapeutic strategy based on the success of replacing missing SA and reducing muscle disease in a relevant mouse model of the human disease. Successful use of SA replacement therapy in humans is believed to depend upon providing steady, long-term exposure to the compound in an extended-release form (such as SA-extended release [SA-ER]), given SA's short half-life. A Phase 2, placebo-controlled study evaluating SA-ER at 2 doses for 48 weeks found that the higher dose of 6 g/day SA-ER stabilized a composite of upper extremity muscle strength (UEC score) compared with placebo or the lower 3 g/day dose; this finding was supported by measurements of functional outcome on the GNE Myopathy Functional Activities Scale (GNEM-FAS). This Phase 3 study is being conducted to further evaluate and confirm the efficacy of SA-ER 6 g/day to preserve upper extremity muscle strength and function. The study will also assess the effects of SA-ER on lower extremity muscle strength and function; patient-reported ability and quality of life; and safety.

**OBJECTIVES:**

**Primary Objective:** Evaluate the effect of 6 g/day SA-ER treatment of subjects with GNEM on upper extremity muscle strength (UEC score) as measured by dynamometry.

**Key Secondary Objectives:** Evaluate the effect of 6 g/day of SA-ER treatment of subjects with GNEM on:

- Lower extremity composite muscle strength score (LEC score) as measured by dynamometry
- Muscle strength in the knee extensors as measured by dynamometry
- Physical functioning as measured using the GNEM-FAS mobility domain score

**Other Secondary Objectives:** Evaluate the effect of 6 g/day of SA-ER treatment of subjects with GNEM on:

- Physical functioning as measured using the GNEM-FAS upper extremity domain score
- Lower extremity function as measured by a timed sit-to-stand test

- Upper extremity function as measured by a timed weighted arm lift test
- Lower extremity function as measured by distance walked in the six-minute walk test (6MWT)

**Tertiary Objectives:** To evaluate the effect of 6 g/day SA-ER treatment of subjects with GNEM on:

- Percent predicted UEC and LEC muscle strength scores as measured by dynamometry
- Muscle strength total force for each individual muscle group comprising the UEC and LEC muscle strength scores, as measured by dynamometry
- Percent predicted strength in each individual muscle group comprising the UEC and LEC muscle strength scores, as measured by dynamometry
- Percent predicted strength in the knee extensors, as measured by dynamometry
- Physical functioning as measured using the GNEM-FAS total score
- Physical functioning as measured using the GNEM-FAS self-care domain score
- Health-related quality of life as measured by the Individual Neuromuscular Quality of Life Questionnaire (INQoL)
- Investigator-assessed symptom severity as measured by the Clinical Global Impression (CGI) Scale
- Changes in serum creatine kinase (CK) as a marker of muscle injury

**Drug Concentration Measurements:** To evaluate the effect of 6 g/day SA-ER treatment of subjects with GNEM on:

- Free SA levels in serum
- Free, total, and bound SA levels in urine

**Safety Objective:** Evaluate the safety of 6 g/day SA-ER treatment of subjects with GNEM

**PRIMARY EFFICACY HYPOTHESIS:**

Treatment with 6 g/day SA-ER tablets is more effective than placebo at maintaining the UEC score based on changes from baseline in bilateral strength recorded in the following muscle groups using dynamometry: gross grip, shoulder abductors, elbow flexors, and elbow extensors.

**STUDY DESIGN AND METHODOLOGY:**

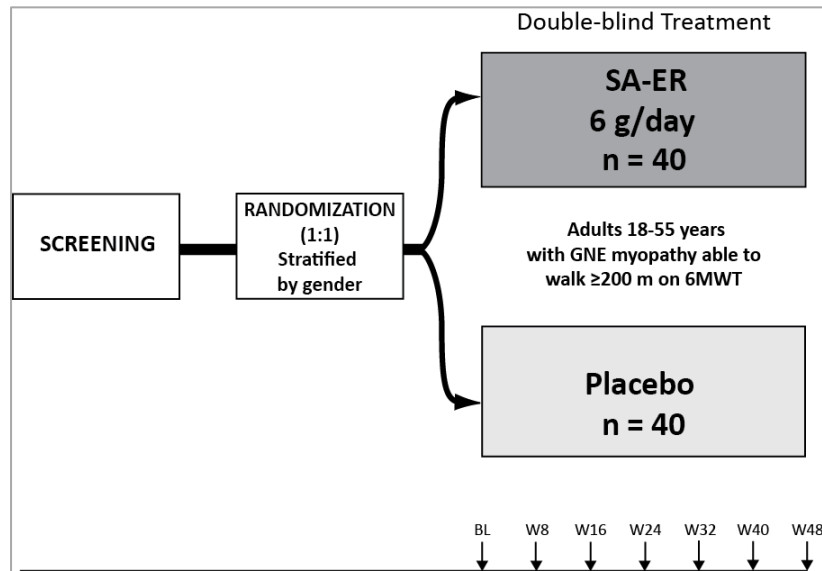
This is a randomized, double-blind, placebo-controlled, multicenter study to assess the clinical effect of 6 g/day SA-ER treatment as compared with placebo in subjects with GNEM. Approximately 80 subjects will be randomized in a 1:1 ratio to receive 6 g/day of SA-ER or matching placebo for 48 weeks. Randomization of subjects will be stratified by gender with a planned enrollment of no more than 60% of subjects of either gender.

Subjects will take 4 tablets (500 mg SA-ER each for 2 g per dose), or matching placebo, 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 8 weeks during the Treatment Period with assessments as outlined in the Schedule of Events (Table 2.1). Subjects who complete the study may be eligible to participate in an open-label extension study.

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.

Figure 2.1 provides a schematic of the study design.

**Figure 2.1: Study Schema**



**NUMBER OF SUBJECTS PLANNED:**

Approximately 80 adult subjects with GNEM are planned for the study.



**DIAGNOSIS AND CRITERIA FOR INCLUSION AND EXCLUSION:**

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

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

1. Male or female, aged 18 – 55 years, inclusive
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. Able to provide reproducible force in elbow flexors (i.e. two dynamometry force values with no more than 15% variability in the dominant arm) at Screening
5. Able to walk a minimum of 200 meters during the 6MWT at Screening without the use of assistive devices, including a cane, crutch(es), walker, wheelchair or scooter (ankle foot orthoses [AFOs] are permitted)
6. Willing and able to comply with all study procedures
7. 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 (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 3 months after last dose of study drug
8. Females of childbearing potential must have a negative pregnancy test at Screening and be willing to have additional pregnancy tests during the study. Females considered not of childbearing potential include those who have been in menopause for at least two years, have had tubal ligation at least one year prior to Screening, or who have had a total hysterectomy or bilateral salpingo-oophorectomy

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

1. Ingestion of N-acetyl-D-mannosamine (ManNAc), 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. History of more than 30 days treatment with SA-ER and/or SA-IR in prior clinical trials in the past year
3. Has had any hypersensitivity to SA or its excipients that, in the judgment of the investigator, places the subject at increased risk for adverse effects
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 SA-ER tablet contains 500 mg of SA in an extended release formulation for a total weight of 1200 mg/tablet. The drug will be administered by the oral route and will be divided into a TID regimen: 4 tablets taken in the morning, early evening, and before bedtime (qHS). The dose should be taken with food (i.e. within 30 minutes after a meal or snack).

**REFERENCE THERAPY, DOSE, AND MODE OF ADMINISTRATION:**

Placebo is matched in appearance and overall size to the SA-ER tablet. Both placebo and SA-ER tablets have a white coating to assure matched color/appearance. The placebo daily dose will be given orally TID as 4 tablets taken in the morning, early evening, and 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 be randomized to receive either 6 g/day SA-ER or placebo.

**CRITERIA FOR EVALUATION:**

**Efficacy:**

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

**Primary Clinical Efficacy Endpoint:**

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

**Key Secondary Clinical Efficacy Endpoints:**

- Lower Extremity Composite Score: Muscle strength based on MVIC against a dynamometer will be measured bilaterally in the following lower extremity muscle groups: knee flexors, hip flexors, hip extensors, hip abductors and hip adductors. The LEC is derived from the sum of the average of the right and left total force values (measured in kg).
- Muscle strength in the Knee Extensors: Bilateral total force defined as the average of the right and left force values (measured in kg).

- GNEM Functional Activities Scale Mobility Domain Score: Physical functioning will be assessed using the Mobility domain of the GNEM-FAS instrument, a disease-specific measure developed to assess the functional impact of changes in muscle strength on mobility (reflective of the lower extremities).

**Other Secondary Clinical Efficacy Endpoints:**

- GNEM Functional Activities Scale Upper Extremity Domain Score: Upper extremity use and function will be assessed using the Upper Extremity domain of the GNEM-FAS instrument, a disease-specific measure developed to assess the functional impact of changes in upper extremity muscle strength.
- Number of Stands in the Sit-to-Stand Test: Lower extremity function will be assessed using a sit-to-stand test. The number of times the subject can rise from a seated to a standing position in a 30-second period will be recorded.
- Number of Lifts in the 30 second Weighted Arm Lift Test: Upper extremity function will be assessed using a weighted arm lift test performed bilaterally. The number of times the subject can raise a 1 kg weight above the head in a 30-second period will be recorded.
- Meters Walked in the Six-Minute Walk Test: The total distance walked (meters) in a six minute period will be measured as well as the percent predicted distance based on normative data for age and gender.

**Tertiary Efficacy Endpoints:**

- Upper Extremity Composite Percent Predicted: The percent predicted total force values will be determined based on reference equations adjusting for age, gender, height, and weight. The percent predicted force will be calculated for each side and the bilateral percent predicted values will be averaged for each upper extremity muscle group. The mean of the four averages in percent predicted scores will be calculated for each subject to create a percent predicted UEC score, and analyzed relative to baseline to create a UEC mean change in percent predicted score.
- Lower Extremity Composite Percent Predicted: The percent predicted total force values will be determined based on reference equations adjusting for age, gender, height, and weight. The percent predicted force will be calculated for each side and the bilateral percent predicted values will be averaged for each lower extremity muscle group. The mean of the five averages in percent predicted scores will be calculated for each subject to create a percent predicted LEC score, and analyzed relative to baseline to create a UEC mean change in percent predicted score.
- Muscle strength (Total Force in kg) for Each Individual Muscle Group: Bilateral total force for each individual muscle group included in the UEC and LEC will be reported.
- Percent of Predicted Muscle Strength in Each Individual Muscle Group: Bilateral percent predicted total force for each individual muscle group included in the UEC and LEC will be reported.
- Percent of Predicted Muscle Strength in the Knee Extensors: Percent predicted total force for the knee extensors will be reported.
- Total Score on the GNEM-FAS
- Self-Care Domain Score on the GNEM-FAS

- **Individual Neuromuscular Quality of Life Questionnaire:** A 45-item self-report questionnaire on the impact of key muscle disease symptoms on the ability to perform basic activities of daily living, functional independence, relationships and overall well-being will be administered. Dimension scores and a Quality of Life score will be calculated.
- **Clinical Global Impression Scale:** Investigator assessment of severity of subject's GNEM using the CGI-improvement scale (CGI-I) during treatment, in 3 target areas.
- **Creatine Kinase Levels:** CK levels in serum will be measured to assess the degree of reduction of CK levels observed as a surrogate for muscle injury.

**Drug Concentration Measurements:**

- **Serum Free Sialic Acid:** Change in free serum SA level.
- **Urine Sialic Acid - Free, Total and Bound:** Changes from baseline in urine free, total and bound SA levels.

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

**Safety:**

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

- Interval history
- Vital signs
- Physical examination results
- Clinical laboratory results
- Suicidal ideation and behavior
- Concomitant medications

**STATISTICAL METHODS:**

**Sample Size:**

Based on the results of the Phase 2 study (UX001-CL201), approximately 80 subjects will be randomized in this Phase 3 study. This sample size will provide 90% power to detect a difference of about 5 kg in the UEC score change from baseline between the SA-ER treatment and the placebo groups, assuming a standard deviation of 6, and a two-sided alpha of 0.05.

**Data Monitoring Committee (DMC):**

An independent and appropriately constituted DMC will act in an advisory capacity to monitor subject safety on a routine basis throughout the trial.

**Analyses Sets:**

**Primary Analysis Set:** The primary efficacy set will include all randomized subjects with a baseline measurement and at least one post-baseline measurement. Each subject will be included in the treatment group assigned at randomization, regardless of the treatment received. This set will be used for the primary analyses of all efficacy endpoints.

**Safety Analysis Set:** The safety analysis set consists of all randomized 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 or urine SA levels.

**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, 6MWT, sit-to-stand, and weighted arm lift 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 Primary Analysis Set and will be stratified by gender. GEE analysis will be performed to compare the two treatment groups with respect to the changes from baseline for the primary endpoint, and all secondary and tertiary efficacy endpoints. Baseline will be included as a covariate in the model. This method will be the primary analysis method for all repeated measures endpoints.

The statistical analyses will be reported using summary tables, figures, and data listings. Statistical tests will be 2-sided at the  $\alpha=0.05$  significance level. Continuous variables will be summarized with means, standard deviations, medians, minimums, and maximums. Categorical variables will be summarized by counts and by percentages of subjects in corresponding categories. The final analyses will be conducted at Week 48.

**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 by treatment group. A by-subject listing will be provided for those subjects who experience a SAE, including death, or experience an AE associated with early withdrawal from the study or study drug treatment.

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

A review of blinded safety data will be conducted by the DMC at least two times a year. Ad hoc meetings will be held if indicated based on observed events.

**Table 2.1: Schedule of Events**

ASSESSMENTS AND EVENTS*	SCREENING <sup>a</sup>	BASELINE <sup>a</sup>	TREATMENT PERIOD <sup>b</sup>							SAFETY FOLLOW-UP <sup>c</sup>
	WEEK -4 to -1	0	4 (TC)	8	16	24	32	40	48/ET <sup>a</sup>	52 (TC)
INFORMED CONSENT	X									
MEDICAL HISTORY, HEIGHT AND WEIGHT <sup>d</sup>	X									
DYNAMOMETRY	X	X		X	X	X	X	X	X	
6-MINUTE WALK TEST (6MWT)	X	X		X	X	X	X	X	X	
SIT-TO-STAND TEST	X	X		X	X	X	X	X	X	
WEIGHTED ARM LIFT TEST	X	X		X	X	X	X	X	X	
GNE MYOPATHY FUNCTIONAL ACTIVITIES SCALE (GNEM-FAS)		X		X	X	X	X	X	X	
INDIVIDUAL NEUROMUSCULAR QUALITY OF LIFE QUESTIONNAIRE (INQOL)		X		X	X	X	X	X	X	
CREATINE KINASE		X		X	X	X	X	X	X	
CLINICAL GLOBAL IMPRESSION SCALE (CGI) <sup>e</sup>		X				X			X	
FREE SERUM SA LEVELS <sup>f</sup>		X		X	X	X	X	X	X	
FREE, TOTAL AND BOUND URINE SA LEVELS <sup>f</sup>		X			X		X		X	
URINE TEST FOR MANNAC <sup>g</sup>	X	X			X		X		X	
INTERVAL HISTORY <sup>h</sup>		X		X	X	X	X	X	X	
PHYSICAL EXAMINATION	X	X <sup>i</sup>		X	X	X <sup>i</sup>	X	X	X <sup>i</sup>	
VITAL SIGNS	X	X		X	X	X	X	X	X	
HEMATOLOGY, CHEMISTRY PANEL, URINALYSIS	X	X		X	X	X	X	X	X	
PREGNANCY TEST	X	X			X		X		X	
CONCOMITANT MEDICATIONS	X	X		X	X	X	X	X	X	X
SUICIDAL IDEATION AND BEHAVIOR <sup>j</sup>	X	X		X	X	X	X	X	X	

ASSESSMENTS AND EVENTS*	SCREENING <sup>a</sup>	BASELINE <sup>a</sup>	TREATMENT PERIOD <sup>b</sup>							SAFETY FOLLOW-UP <sup>c</sup>
	WEEK -4 to -1	0	4 (TC)	8	16	24	32	40	48/ET <sup>a</sup>	52 (TC)
ADVERSE EVENTS	X	X	X <sup>b</sup>	X	X	X	X	X	X	X
TREATMENT DISPENSED <sup>k</sup>		X		X	X	X	X	X		
TREATMENT COMPLIANCE				X	X	X	X	X	X	

\* Refer to Study Reference Manual for recommended timing and order of assessments to be administered at each study visit

- a. Potential subjects will be screened approximately seven days (up to 28 days) before the Baseline Visit. Study drug will be dispensed only after all study procedures at the Baseline Visit have been performed. For subjects who discontinue prior to completing the study, every reasonable effort should be made to perform the Early Termination (ET) procedures within four weeks of discontinuation.
- b. Visits occur every 8 weeks  $\pm$  5 days; subjects will be contacted by telephone call (TC) at Week 4 for abbreviated safety assessment. Additional unscheduled telephone calls may also occur for subject follow up. Unscheduled visits are allowed for safety or administrative purposes. Notify the medical monitor before an unscheduled visit.
- c. 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 the extension study, UX001-CL302. The site personnel will initiate a safety follow-up telephone call 28 days (+5 days) after a subject's last dose of study drug to collect information on any ongoing or new AEs, serious adverse events (SAEs), and concomitant medications. Appropriate follow-up should continue until all safety concerns, in the Investigator's opinion, are resolved.
- d. Medical history will include a detailed GNEM disease-specific medical history.
- e. CGI-Severity scale will be assessed at Baseline (Week 0) along with identification of 3 target areas for disease improvement; CGI-Improvement scale will be assessed at each subsequent visit using 3 target areas identified at Baseline.
- f. Pre-dose blood samples and first-morning void urine will be collected to assess trough SA levels; record volume of urine collected.
- g. An aliquot from the urine sample provided for the standard urinalysis will be used for assessment of ManNAc.
- h. Interval history will include any signs, symptoms, or events (i.e. falls) experienced by the subject since the prior study visit that are not related to study procedure(s) performed at prior study visits or study drug. Interval history may include exacerbation or improvement in existing medical conditions (including the clinical manifestations of GNEM) that might interfere with study participation, safety, and/or positively or negatively impact performance of functional assessments.
- i. The physical examinations at Baseline and Weeks 24 and 48 will be complete, including a neurological examination; all others will be brief physical examinations.
- j. Baseline/Screening C-SSRS administered at Screening and Baseline visits. Since Last Visit C-SSRS administered at all subsequent visits.
- k. Subjects should be instructed to return unused study drug and packaging to every visit.



### 3 TABLE OF CONTENTS

1	TITLE PAGE .....	1
2	SYNOPSIS.....	4
3	TABLE OF CONTENTS.....	14
4	LIST OF ABBREVIATIONS AND DEFINITION OF TERMS .....	19
5	INTRODUCTION .....	22
5.1	Overview of GNE Myopathy.....	23
5.2	Brief Overview of SA-ER Development .....	24
5.2.1	Brief Description of SA-ER .....	24
5.2.1.1	Mechanism of Action in GNE Myopathy.....	25
5.2.2	Nonclinical Studies.....	26
5.2.3	Previous Clinical Studies.....	27
5.2.4	Summary of Overall Risks and Potential Benefits .....	29
5.3	Study Rationale .....	30
5.4	Primary Efficacy Hypothesis .....	30
6	STUDY OBJECTIVES.....	31
7	INVESTIGATIONAL PLAN.....	32
7.1	Overall Study Design and Plan .....	32
7.2	Discussion of Study Design, Including Choice of Control Group.....	33
7.3	Selection of Study Population.....	34
7.3.1	Inclusion Criteria.....	34
7.3.2	Exclusion Criteria.....	35
7.3.3	Removal of Subjects from Therapy or Assessment .....	36
7.3.3.1	Stopping Rules .....	37
7.4	Treatments.....	37
7.4.1	Investigational Product.....	37
7.4.2	Reference Therapy .....	37



7.4.3	Selection of Doses and Study Duration.....	38
7.4.4	Method of Assigning Subjects to Treatment Groups .....	39
7.4.5	Blinding .....	39
7.4.6	Prior and Concomitant Therapy .....	39
7.4.6.1	Prohibited Medications .....	39
7.4.6.2	Permitted Medications .....	40
7.4.7	Treatment Compliance .....	40
7.5	Study Procedures and Assessments .....	40
7.5.1	Study Schedule .....	41
7.5.1.1	Screening Period .....	41
7.5.1.2	Baseline Visit .....	41
7.5.1.3	Treatment Period.....	41
7.5.1.4	End of Study/Early Termination Visit (Week 48/ET) .....	41
7.5.1.5	Safety Follow-up Period .....	41
7.5.2	Efficacy Measures .....	42
7.5.2.1	Dynamometry .....	42
7.5.2.2	Knee Extensor Muscle Strength.....	43
7.5.2.3	GNEM Functional Activities Scale .....	44
7.5.2.4	Sit-to-Stand Test .....	44
7.5.2.5	Weighted Arm Lift Test.....	44
7.5.2.6	Six Minute Walk Test.....	45
7.5.2.7	Individual Neuromuscular Quality of Life Questionnaire .....	45
7.5.2.8	Clinical Global Impression Scale.....	45
7.5.2.9	Creatine Kinase Levels .....	46
7.5.3	Drug Concentration Measurements.....	46
7.5.4	Urine Testing for ManNAc .....	46
7.5.5	Safety Measures & General Assessments .....	47

7.5.5.1	Medical History .....	47
7.5.5.2	Height and Weight .....	47
7.5.5.3	Interval History .....	47
7.5.5.4	Physical Examination.....	47
7.5.5.5	Vital Signs.....	48
7.5.5.6	Clinical Laboratory Tests for Safety.....	48
7.5.5.7	Pregnancy Testing.....	50
7.5.5.8	Suicidal Ideation and Behavior.....	51
7.5.5.9	Concomitant Medications .....	51
7.5.5.10	Adverse Events .....	51
7.5.6	Appropriateness of Measures .....	52
7.6	Statistical Methods and Determination of Sample Size.....	52
7.6.1	Determination of Sample Size.....	53
7.6.2	Subject Information .....	53
7.6.3	Populations Analyzed.....	53
7.6.4	Efficacy Analysis .....	53
7.6.4.1	Primary Efficacy Endpoint and Analysis.....	54
7.6.4.2	Secondary Endpoints and Analyses .....	54
7.6.4.3	Tertiary Endpoints and Analysis.....	55
7.6.5	Analyses of Drug Concentration Measurements.....	56
7.6.6	Safety Analyses .....	56
7.6.7	Data Monitoring Committee .....	57
8	STUDY CONDUCT.....	58
8.1	Ethics.....	58
8.1.1	Institutional Review Board or Ethics Committee.....	58
8.1.2	Ethical Conduct of Study .....	58
8.1.3	Subject Information and Consent.....	58

8.2	Investigators and Study Administrative Structure .....	59
8.3	Investigational Product Accountability.....	59
8.4	Data Handling and Record Keeping .....	60
8.4.1	Case Report Forms and Source Documents .....	60
8.4.2	Data Quality Assurance.....	60
8.4.3	Record Retention.....	61
8.5	Reporting and Follow-up of Adverse Events.....	61
8.5.1	Definition of Adverse Events .....	61
8.5.2	Severity of Adverse Events .....	62
8.5.3	Relationship of Adverse Events to Study Drug.....	63
8.5.4	Adverse Event Reporting .....	63
8.5.4.1	General .....	63
8.5.4.2	Serious Adverse Events, Serious Adverse Drug Reactions, and Requirements for Immediate Reporting.....	64
8.5.4.3	Pregnancy Reports .....	64
8.5.5	Communication Plan .....	64
8.5.5.1	Review of Safety Data .....	64
8.5.5.2	Adverse Drug Reaction Reporting.....	65
8.5.6	Urgent Safety Measures .....	65
8.5.7	Safety Contact Information .....	66
8.6	Financing and Insurance .....	66
8.7	Publication Policy .....	66
9	REFERENCES .....	67
10	SIGNATURE PAGE .....	70

**List of Tables**

Table 2.1: Schedule of Events.....12  
Table 7.5.5.6.1: Clinical Laboratory Assessments for Safety.....49  
Table 7.5.5.6.1.1: Volume of Blood to Be Drawn From Each Subject .....50

**List of Figures**

Figure 2.1: Study Schema.....6  
Figure 5.2.1.1.1: The Biosynthetic Pathway of Sialic Acid in its Subcellular  
Locations.....26  
Figure 7.1.1: Study Schema.....32

#### 4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

##### Abbreviations

6MWT	Six Minute Walk Test
AE	adverse event
AFO	ankle foot orthosis/orthoses
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATS	American Thoracic Society
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CGI	Clinical Global Impression
cGMP	Current Good Manufacturing Practices
CK	creatine kinase
CRF	Case Report Form
C-SSRS	Columbia-Suicide Severity Rating Scale
DMC	Data Monitoring Committee
DMRV	distal myopathy with rimmed vacuoles
EC	Ethics Committee
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEE	generalized estimating equation
GI	gastrointestinal
GlcNAc	N acetyl-glucosamine
GNE	glucosamine (UDP-N-acetyl)-2-epimerase
GNE-DMP	GNE Myopathy Disease Monitoring Program
GNE/MNK	glucosamine (UDP-N-acetyl)-2-epimerase/N-acetylmannosamine kinase
GNEM	GNE Myopathy
GNEM-FAS	GNE Myopathy Functional Activities Scale
hERG	human ether-à-go-go-related gene
HIBM	hereditary inclusion body myopathy
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	informed consent form

ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IND	Investigational New Drug (application)
INQoL	Individual Neuromuscular Quality of Life Questionnaire
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine system
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	pharmacodynamic
PK	pharmacokinetic(s)
PT	Preferred Term
qHS	at the time of sleep (i.e., at bedtime)
QSM	quadriceps sparing myopathy
RBC	red blood cell
RSI	Reference Safety Information
SA	sialic acid
SAE	serious adverse event
SA-ER	Sialic Acid-Extended Release
SA-IR	Sialic Acid Immediate Release
SAP	Statistical Analysis Plan
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

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

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

Ultragenyx has developed SA-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). SA-ER was developed to improve the stability of exposure to SA and allow more appropriate dosing and efficient substrate replacement. The SA-ER formulation was evaluated in an initial Phase 1 study to establish the safety and pharmacokinetic (PK) profile of a single dose and 7 days of repeat dosing in SA-deficient GNEM patients. The study drug was well tolerated at all dose levels. There were no serious adverse events (SAEs), and all adverse events (AEs) were mild to moderate with no dose relationship or pattern.

A Phase 2 randomized, placebo-controlled study evaluated chronic dosing of SA-ER at two dose levels to establish the pharmacodynamic (PD) effects of SA on sialylation, identify the appropriate dose level, and provide insight into clinical efficacy and safety. Data from the Phase 2 study demonstrated efficacy and acceptable safety profile at the higher 6 g/day SA-ER dose level. The degree of effect observed was dependent on serum SA levels suggesting the potential to optimize the therapeutic index by increasing SA exposure. An extension of the Phase 2 study was designed in two parts to provide additional long-term safety and clinical efficacy data 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 SA ER tablets with an immediate-release capsule formulation of SA (SA-IR[Part II]). (Refer to the Investigator's Brochure (IB) for additional details on SA-IR.) Data on combination SA-ER/SA-IR treatment at 12 g/day suggest a modest further improvement in UEC strength over the 6 g/day dose, although the result was not dramatically better, and there was an



increase in AEs related to gastrointestinal (GI) tolerability at the higher 12 g/day dose. Based on the totality of the data the 6 g/day dose demonstrated the optimal benefit to risk profile and thus will be tested in Phase 3.

Ultragenyx is also sponsoring a GNEM Disease Monitoring Program (GNEM-DMP) which includes a disease registry (a longitudinal patient reported disease outcome survey) and a natural history study (a physician-reported protocol-driven formal study). The GNEM-DMP is being conducted in parallel with the SA clinical development program to collect data on disease characteristics and progression.

This Phase 3 randomized, placebo-controlled study is designed to confirm the long-term safety and efficacy of 6 g/day SA-ER tablets in GNEM patients.

## 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. Since that time, patients have been identified worldwide, including those of Italian, Japanese, Thai, Indian, American and African origin ([Huizing et al. 2009](#)). GNEM is a rare disease; the incidence and prevalence is low but exact numbers are not available. 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 pathophysiological effect of decreased sialylation on proteins or lipids is still debated.

The clinical course is similar and includes an onset usually after age 20 (mean 26 years, range 15–40 years) though it 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 some fatty replacement infiltration 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. 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. 1987); (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. Electromyography in GNEM is abnormal with spontaneous fibrillations consistent with denervation, however nerve conduction is generally normal (Sadeh et al. 1993); (Mizusawa et al. 1987). Imaging studies of the muscle by computed tomography (Sadeh et al. 1993); (Mizusawa et al. 1987) 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 SA-ER Development

SA-ER tablets are in development as a treatment for GNEM. The scientific rationale for SA substrate replacement therapy is primarily based on the nature of the underlying genetic defect supported by proof of concept work in a knockout mouse which models the muscle disease and pathology of HIBM (Malicdan et al. 2009). Nonclinical studies have been conducted in HIBM mice and multiple species of normal animals. Three clinical studies have been conducted to characterize the PK, tolerability, safety and efficacy of SA replacement in GNEM patients.

A brief overview of existing information on SA-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 SA-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.

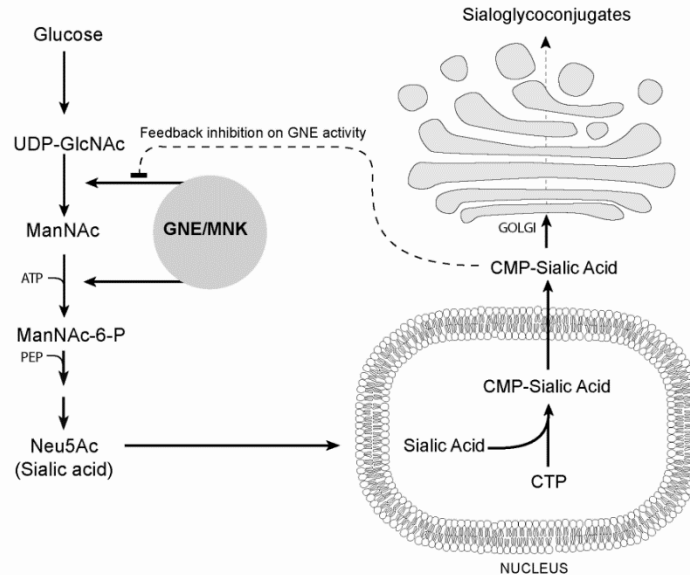
The active SA pharmaceutical ingredient is produced synthetically in an enzyme-catalyzed two step reaction where N acetyl-glucosamine (GlcNAc) is converted into SA. No mammalian sourced products are used in the production of SA. The product is purified and crystallized yielding high purity SA which is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

SA-ER 500 mg tablets are white to off-white, film-coated, extended-release, oval tablets that 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 SA. Tablets are manufactured by a formulation process using wet aqueous granulation; the blend is then dried and compressed into tablet cores. The tablet cores are coated with Opadry II, a non-functional aqueous film coating. SA-ER 500 mg tablets are 1200 mg in total weight.

#### **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 SA-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  $6 \times 10^{-3}$  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 SA 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 SA-ER tablets was conducted in GNEM subjects. Twenty-seven (27) subjects were assigned to treatment; 26 were dosed with SA-ER and completed dosing. Subjects received SA-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 SA-ER showed that trough levels could be maintained above the pre-dose baseline level, as expected for a sustained release formulation.

SA-ER was well tolerated in this group of GNEM patients 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 dose and PD of SA-ER tablets in 47 GNEM patients (Argov et al. 2014). Subjects were randomized to receive placebo or 3 g/day or 6 g/day SA-ER. After 24 weeks, placebo subjects crossed over (blinded) to either 3 g/day or 6 g/day SA-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; 5.5% relative difference from baseline;  $p=0.040$ ). At Week 48, a statistically significant difference between the combined 6 g/day group and the combined 3 g/day group was observed (+3.44 kg; 8.5% relative difference from baseline;  $p=0.0033$ ). 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 (+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; a positive trend in total ( $p=0.086$ ), mobility ( $p=0.087$ ), and upper extremity scores ( $p=0.096$ ) in the combined 6 g/day vs 3 g/day groups was observed at Week 48 when analyzed by the pre-specified ANCOVA analysis. Changes in total, mobility, and upper extremity scores were significant in the combined 6 g/day vs 3 g/day groups when analyzed in a post-hoc analysis.

SA-ER appeared to be well tolerated with no SAEs reported in either dose group and no dose-dependent TEAEs identified. Common TEAEs included headache, arthralgia, back pain, fatigue, diarrhea, 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 SA-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 SA-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, the majority of subjects will have their dose reduced from 12 g/day to 6 g/day. The treatment-naïve group and a small subset of rollover subjects who showed potential clinical benefit at 12 g/day will have the option to remain on the higher dose.



Evaluations include safety, changes in clinical endpoints such as muscle strength, mobility, and function, and changes in exploratory serum biomarkers. Data from a 24-week assessment in Part II suggest that the 12 g/day dose does not convey dramatically better efficacy than the 6 g/day dose in muscle strength or clinical endpoints. 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.

#### **5.2.4 Summary of Overall Risks and Potential Benefits**

Since SA is a normal body compound with native pathways for degradative metabolism and rapid renal clearance, there is no evidence or expectation of a significant safety issue with SA replacement therapy. Data from nonclinical and clinical studies to date suggest SA-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 other SAEs. The majority of subjects had TEAEs that were graded as mild to moderate severity. A single subject in the 3 g/day SA-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 SA-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 SA-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 patients with GNEM, replacement of the substrate SA has the potential to restore normal sialylation of muscle glycoproteins and glycolipids, which could improve the function of muscle and limit the loss of muscle strength. It is not clear how much the effects of GNEM are reversible or if and how fast reversal of muscle disease might occur. The data in

the HIBM mouse model suggest that over a one-year period, substantial beneficial effects on the pathology of the disease are possible. However, the extent to which advanced disease can be improved, or prevention of disease progression is unknown.

In clinical studies conducted to date, 6 g/day SA-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 severe, progressive myopathy caused by a defect in the biosynthetic pathway for sialic acid (SA). Substrate replacement is a potential therapeutic strategy based on the success of replacing missing SA and reducing muscle disease in a relevant mouse model of the human disease. A Phase 2, placebo-controlled study evaluating SA extended release (SA-ER) at 2 doses for 48 weeks found that the higher dose of 6 g/day SA-ER stabilized the UEC score compared with placebo or the lower 3 g/day dose; this finding was supported by measurements of functional outcome on the GNEM-FAS. This Phase 3 study is being conducted to further evaluate and confirm the efficacy of 6 g/day SA-ER tablets to preserve upper extremity muscle strength and function. The study will also assess the effects of SA-ER on lower extremity muscle strength and function; patient-reported ability and health-related quality of life; and safety.

### **5.4 Primary Efficacy Hypothesis**

Treatment with 6 g/day SA-ER tablets is more effective than placebo at maintaining the UEC score based on changes from baseline in bilateral strength recorded in the following muscle groups using dynamometry: gross grip, shoulder abductors, elbow flexors, and elbow extensors.



## 6 STUDY OBJECTIVES

**Primary Objective:** Evaluate the effect of 6 g/day SA-ER treatment of subjects with GNEM on upper extremity muscle strength (UEC score) as measured by dynamometry.

**Key Secondary Objectives:** Evaluate the effect of 6 g/day of SA-ER treatment of subjects with GNEM on:

- Lower extremity composite muscle strength score (LEC score) as measured by dynamometry
- Muscle strength in the knee extensors as measured by dynamometry
- Physical functioning as measured using the GNEM-FAS mobility domain score

**Secondary Objectives:** Evaluate the effect of 6 g/day of SA-ER treatment of subjects with GNEM on:

- Physical functioning as measured using the GNEM-FAS upper extremity domain score
- Lower extremity function as measured by a timed sit-to-stand test
- Upper extremity function as measured by a timed weighted arm lift test
- Lower extremity function as measured by distance walked in the 6MWT

**Tertiary Objectives:** To evaluate the effect of 6 g/day SA-ER treatment of subjects with GNEM on:

- Percent predicted UEC and LEC muscle strength scores as measured by dynamometry
- Muscle strength total force for each individual muscle group comprising the UEC and LEC muscle strength scores, as measured by dynamometry
- Percent predicted in each individual muscle group comprising the UEC and LEC muscle strength scores, as measured by dynamometry
- Percent predicted strength in the knee extensors, as measured by dynamometry
- Physical functioning as measured using the GNEM-FAS total score
- Physical functioning as measured using the GNEM-FAS self-care domain score
- Health-related quality of life as measured by the Individual Neuromuscular Quality of Life Questionnaire (INQoL)
- Investigator-assessed symptom severity as measured by the Clinical Global Impression (CGI) Scale
- Changes in CK as a marker of muscle injury

### **Drug Concentration Measurements**

- Free SA levels in serum
- Free, total, and bound SA levels in urine

**Safety Objective:** Evaluate the safety of 6 g/day SA-ER treatment of subjects with GNEM.

## 7 INVESTIGATIONAL PLAN

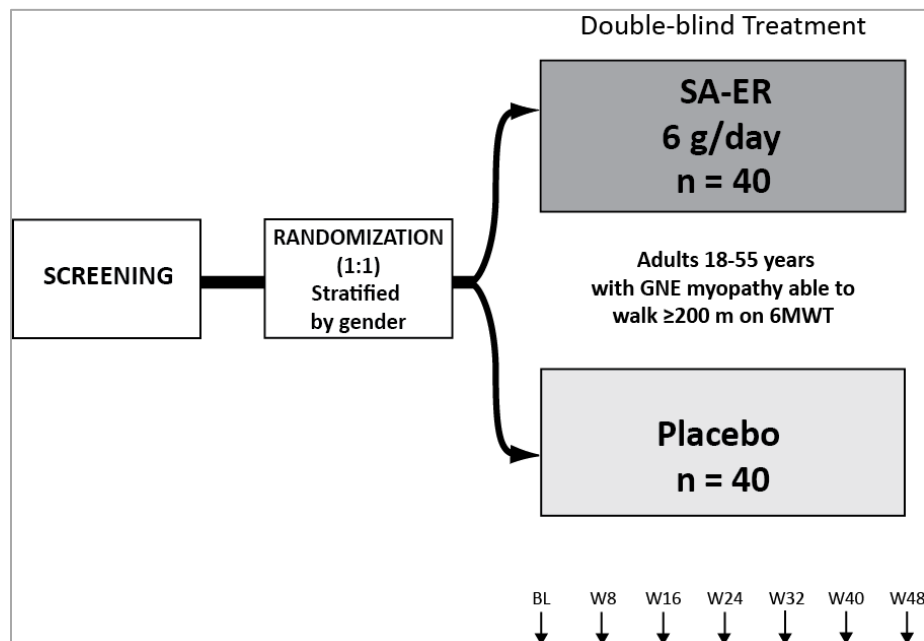
### 7.1 Overall Study Design and Plan

This is a randomized, double-blind, placebo-controlled, multicenter study to assess the clinical effect of 6 g/day SA-ER treatment as compared with placebo in subjects with GNEM. Approximately 80 subjects will be randomized in a 1:1 ratio to receive 6 g/day of SA-ER or matching placebo for 48 weeks. Randomization of subjects will be stratified by gender with a planned enrollment of no more than 60% of subjects of either gender.

Subjects will take 4 tablets (500 mg SA-ER each for 2 g per dose), or matching placebo, orally 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 8 weeks during the Treatment Period with assessments as outlined in the Schedule of Events (Table 2.1). Subjects who complete the study may be eligible to participate in an open-label extension study.

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. Figure 7.1.1 provides a schematic of the study design.

**Figure 7.1.1: Study Schema**



## 7.2 Discussion of Study Design, Including Choice of Control Group

This Phase 3 study is designed to confirm the long-term safety and efficacy of 6 g/day SA-ER in GNEM patients. The study will be conducted as a randomized, double-blind, placebo-controlled study to assure objectivity and maximize validity in the assessment of changes related to efficacy. The control group will be a parallel group receiving a placebo tablet formulated comparably to the SA-ER active investigational product.

The study will assess long-term effects of SA-ER on clinical measures of muscle strength, mobility, function, ability and health-related quality of life. The primary efficacy endpoint in the study, change in UEC score over 48 weeks as measured by dynamometry, is representative of muscle strength and relevant to the clinical pathology and disease progression in GNEM. In the UX001-CL201 Phase 2 study, the UEC for the combined 6 g/day group showed a modest increase and a statistically significant difference relative to the decline in strength observed in the combined 3 g/day group. The 6MWT has been a useful measurement of lower extremity function in certain neuromuscular diseases and is included in this study as a secondary endpoint. For GNEM, the 6MWT was not chosen as the primary endpoint because of limitations of its use and interpretation in this disease. This is due to the pattern of muscle weakness in GNEM. The ankle muscles including dorsiflexors and plantarflexors are typically severely atrophied in patients with GNEM and these muscles are critical in allowing the foot to spring forward and propel the patient while walking. Furthermore, the lack of strength in these muscles drives patients to use ankle-foot orthoses (AFOs), but these rigid devices also limit the ability to increase ambulatory speed. Lastly, data from the UX001-CL201 study indicates that hip flexors are nearly absent at the time of enrollment. These muscles are critical in swinging the entire leg forward to initiate walking, again limiting speed of ambulation. This lack of ability to increase speed is supported by the baseline data in the UX001-CL201 study where the comfortable walking speed was 61% of predicted normal whereas the maximum pace was only 46% predicted normal.

Another reason for the lack of ability to increase speed may be the fear of falling. In the UX001-CL201 study, more than 70% of patients who were able to walk more than 200m reported frequent falls prior to enrollment. Thus, walking tests such as the 6MWT, based on the biology and clinical characteristics of the disease, may lack the sensitivity or specificity to properly quantify any potential treatment effect.

The study population comprises adult GNEM patients since the onset of disease usually occurs after age 20. The study seeks to balance gender effects by stratifying randomization based on gender, and targeting enrollment of no more than 60% of one gender. Enrolled subjects will have a confirmed diagnosis of GNEM, however the study population is inherently limited to only those subjects able to reliably perform dynamometry and walk a minimum of 200 meters without the use of assistive devices in a 6MWT. While these inclusion criteria ensure reproducible data, the study population may represent a less severe GNEM disease state due to these restrictions.

The 48-week treatment duration is intended to confirm whether the 6 g/day dose level is safe for long-term use and provide sufficient characterization of sustained clinical effects. In prior studies of comparable muscle diseases such as late-onset Pompe disease, the maximum treatment effect for the 6MWT was achieved in the first six months, with a plateau observed over the remaining 12 months of the study. The amount of time required to obtain reversal of GNEM disease in humans is unknown, but it would be unlikely to observe such changes after 6-12 months of treatment. In a previous Phase 2 study in GNEM, results after 48 weeks of treatment were similar to those observed at the 24-week interim analysis.

### **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 are unable 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.

To provide reliable data on the efficacy of SA-ER treatment in improving muscle strength and function, eligible subjects must be able to provide reproducible dynamometry results in the dominant elbow flexor. As an indicator of lower muscle group disease involvement, subjects must also independently walk a minimum of 200 meters without the use of assistive devices during the 6MWT. To avoid imbalance in the study population, the study will seek to enroll no more than 60% of either gender, and will stratify randomization based on gender.

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. For safety purposes, individuals with impaired liver and renal function are not eligible to participate in the study.

#### **7.3.1 Inclusion Criteria**

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

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

- 1) Male or female, aged 18 – 55 years, inclusive
- 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) Able to provide reproducible force in elbow flexors (i.e. two dynamometry force values with no more than 15% variability in the dominant arm) at Screening
- 5) Able to walk a minimum of 200 meters during the 6MWT at Screening without the use of assistive devices, including a cane, crutch(es), walker, wheelchair or scooter (AFOs are permitted)
- 6) Willing and able to comply with all study procedures
- 7) 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 (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 3 months after last dose of study drug
- 8) 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) History of more than 30 days treatment with SA-ER and/or SA-IR in prior clinical trials in the past year
- 3) Has had any hypersensitivity to SA or its excipients that, in the judgment of the investigator, places the subject at increased risk for adverse effects
- 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 within the defined follow-up period stated in Section 7.5.1.5, 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**

A Data Monitoring Committee (DMC) will be constituted for Study UX001-CL301 and will act in an advisory capacity to monitor the safety of SA-ER on a routine basis throughout the trial (Section 7.6.7). The DMC may provide advice to Ultragenyx in any determination of whether study enrollment should be paused or if the study should be stopped.

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 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 80 subjects will be randomized 1:1 to one of two treatment groups:

- SA-ER tablets, 6 g/day divided TID
- Matched placebo tablets, divided TID

### **7.4.1 Investigational Product**

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

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

### **7.4.2 Reference Therapy**

Placebo is matched in appearance and overall size to the SA-ER tablet. Both placebo and SA-ER have a white coating to assure matched color/appearance. The placebo daily dose will be given orally TID as 4 tablets taken in the morning, early evening, and qHS. The dose should be administered with food (i.e. within 30 minutes of a meal or snack).



### 7.4.3 Selection of Doses and Study Duration

#### *Selection of Doses:*

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

The Phase 2, randomized, placebo-controlled study (UX001-CL201) evaluated treatment with SA-ER at two dose levels of 3 g/day and 6 g/day for 48 weeks. In this study, the higher dose of 6 g/day stabilized upper extremity muscle strength compared with placebo or the lower 3 g/day dose; this finding was 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 SA-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 SA treatment at 12 g/day. No substantial or dramatic 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 SA-ER dose has been selected for further study as the minimum effective dose with a maximal or near maximal 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 56 weeks, including up to 4 weeks between Screening and Baseline visits, a treatment duration of 48 weeks, and a Safety Follow-up Call occurring approximately 4 weeks after last study drug administration. Subjects who complete the study may be eligible to participate in an open-label extension study.

All subjects will be randomized to receive 6 g/day SA-ER or placebo during the 48-week Treatment Period. The 48-week treatment duration is also intended for collection of safety data on the SA-ER tablets for long-term use and to provide sufficient insight on sustained clinical effects and improvements in adult GNEM patients.



#### **7.4.4 Method of Assigning Subjects to Treatment Groups**

Subjects will be enrolled in the study and sequentially assigned an identification number. Approximately 80 eligible subjects will be randomized via an Interactive Web Randomization System (IWRS) and assigned in a 1:1 ratio to receive 6 g/day of SA-ER or matching placebo for 48 weeks. Randomization of subjects will be stratified by gender with a planned enrollment of no more than 60% of subjects of either gender.

#### **7.4.5 Blinding**

The study will be conducted as a randomized, double-blind, placebo-controlled study. Double-blind conditions will be established so that neither the sponsor, subject, or site personnel involved in study conduct will know the identity of a subject's treatment. Study parameters to achieve and maintain the double-blind status of the study include:

- Sequential assignment of subject numbers
- Management of subject treatment assignment via an IWRS
- Labeling of study drug with the study number and a unique kit number
- Packaging and delivery of study drug supplies to sites in a manner that maintains blinding of site personnel
- Matched appearance of investigational product and placebo

The Investigator and site personnel will remain blinded to the randomization code during the study. Treatment assignment for an individual subject should be unblinded by the Investigator only in an emergency, and only if knowledge of the treatment assignment is urgently needed for the clinical management or welfare of the subject. Treatment should be provided in accordance with the medical condition and with regard to the information provided in the IB. The Investigator should contact the medical monitor or project manager before unblinding, when possible, but priority should be given to treatment of the subject.

The Investigator must record the date and reason for revealing the blinded treatment assignment for that subject in the IWRS and in the source documents. Treatment assignment may be unblinded by the Sponsor to satisfy expedited safety reporting requirements of regulatory authorities. The system to unblind an assignment will be maintained and executed through an IWRS which will be available 24 hours a day, 7 days a week.

#### **7.4.6 Prior and Concomitant Therapy**

##### **7.4.6.1 Prohibited Medications**

Patients may not be enrolled if they have a history of more than 30 days treatment with SA 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.**

#### **7.4.6.2 Permitted Medications**

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

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

#### **7.4.7 Treatment Compliance**

Site personnel will maintain a record of all medication dispensed to each subject. Subjects will be instructed to bring all unused study drug and product packaging to every visit. Drug accountability will be assessed by site personnel and recorded. All used containers and unused study drug must be returned at in-clinic visits. Measurements of trough free SA levels in the serum and urine may also 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-CL301, along with timing of assessments, are provided in the Schedule of Events ([Table 2.1](#)). Refer to the Study Reference 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 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. 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 within 7 to 28 days of the Screening visit. Subjects will be randomized only after inclusion/exclusion criteria have been confirmed. Baseline visit (Week 0) assessments must be completed prior to first dose of study drug.

#### **7.5.1.3 Treatment Period**

Subjects will be contacted by telephone four weeks after the Baseline Visit for an abbreviated safety follow-up. Subjects will return to the clinic at 8-week intervals ( $\pm 5$  days) throughout the Treatment Period (Weeks 0 – 48).

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

All randomized subjects who complete the study or discontinue early should complete the Week 48/ET visit.

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.

#### **7.5.1.5 Safety Follow-up Period**

A safety follow-up call should be initiated by the site personnel 28 days (+5 days) after a subject's last dose of study drug to collect information on any ongoing or new AEs, serious adverse events (SAEs), and concomitant medications. Appropriate follow-up should continue until all safety concerns, in the Investigator's opinion, are resolved.

This call should 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.

Subjects who have completed the Week 48 Visit of this study, meet the requirements of the extension study, and choose to enroll in the open-label extension study, UX001-CL302, will not be required complete the follow-call.

## **7.5.2 Efficacy Measures**

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

The primary efficacy endpoint in this study, UEC as derived from dynamometry, will provide a clinical measure of muscle function and strength. The primary efficacy endpoint will be the change from baseline in UEC score for the SA-ER group compared with placebo based on the overall trend over the treatment period (Section 7.6.4). The primary efficacy measure will be supported by multiple secondary and tertiary endpoints, including GNEM-FAS mobility and upper extremity domain scores, LEC, multiple measures of lower extremity strength and function, clinical performance tests to assess mobility and functional abilities, health-related quality of life assessments, and biochemical markers. Secondary and tertiary endpoints and associated analyses are described in Sections 7.6.4.2 and 7.6.4.3, respectively. The following section describes the assessments that will be performed throughout the study to derive primary, secondary, and tertiary endpoints.

### **7.5.2.1 Dynamometry**

Dynamometry of multiple muscle groups will be used to derive the primary efficacy endpoint as well as multiple secondary and tertiary efficacy endpoints. Dynamometry sessions will occur at each visit beginning with the Screening Visit to serve as training and ensure the subject meets eligibility criteria.

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, elbow flexors, elbow extensors, hip abductors, hip adductors, hip flexors, hip extensors, knee flexors and knee extensors. A hand dynamometer will be used to assess gross grip strength.

Each effort will last approximately three seconds with a slow build to a maximum voluntary force. Strength in the elbow flexors and elbow extensors will be measured with the subject lying in a supine position on an examination table. Strength in the hip extensors will be measured with the subject leaning over an examination table in a prone position. All other muscle groups will be tested with the subject in a sitting position. All measurements will be taken bilaterally; the dominant side will be noted in the CRF. Three tests will be administered in an attempt to obtain two force values within approximately 15% of each other for each muscle group. 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 as secondary or tertiary endpoints (Section 7.6.4).

#### **7.5.2.1.1 Primary Efficacy Endpoint: Upper Extremity Composite Score**

Muscle strength based on the MVIC against a dynamometer will be measured bilaterally in the following upper extremity muscle groups: gross grip, shoulder abductors, elbow flexors, and elbow extensors. The UEC is derived from the sum of the average of the right and left total force values (measured in kg) for each muscle group. The comparison of the two treatment groups will be based on the change from baseline in mean UEC score between SA-ER and placebo using generalized estimating equation (GEE) repeated measures with baseline as a covariate.

Additional UEC-related parameters will serve as tertiary efficacy endpoints. The percent predicted total force values will be determined based on reference equations adjusting for age, gender, height, and weight. The percent predicted force will be calculated for each side and the bilateral percent predicted values will be averaged for each upper extremity muscle group (gross grip, shoulder abductors, elbow flexors, and elbow extensors). The mean of the four averages in percent predicted scores will be calculated to create a percent predicted UEC score, and analyzed relative to baseline to create a UEC mean change in percent predicted score. The change in mean percent predicted UEC score between SA-ER and placebo will be compared using the GEE repeated measures analysis.

#### **7.5.2.1.2 Lower Extremity Composite Score**

Muscle strength based on MVIC against a dynamometer will be measured bilaterally in the following lower extremity muscle groups: knee flexors, hip flexors, hip extensors, hip abductors and hip adductors. Each muscle group is the average of the right and left total values (measured in kg). The LEC score is derived from the sum of all muscle groups and is a key secondary endpoint. The percent predicted total force values for the LEC will also be determined and analyzed as a tertiary endpoint. The percent predicted force will be calculated for each side and the bilateral percent predicted values will be averaged for each lower extremity muscle group (knee flexors, hip flexors, hip extensors, hip abductors and hip adductors). The mean of the five averages in percent predicted scores will be calculated to create a percent predicted LEC score, and analyzed relative to baseline to create a LEC mean change in percent predicted score.

#### **7.5.2.2 Knee Extensor Muscle Strength**

The knee extensors (quadriceps) are widely recognized to be spared in GNEM relative to other lower extremity muscle groups, making it a defining feature of the disease and instrumental in making a differential diagnosis. Knee extensor strength based on MVIC

against a dynamometer will be measured bilaterally as described in Section 7.5.2.1 and is a key secondary endpoint. The percent predicted total force values for the knee extensors will also be determined and analyzed as a tertiary endpoint.

### **7.5.2.3 GNEM Functional Activities Scale**

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: mobility (a key secondary endpoint), upper extremity (secondary endpoint), and self-care (tertiary endpoint); scores for each domain and a total score (tertiary endpoint) will be obtained. The GNEM-FAS will be administered at the Baseline Visit and Weeks 8, 16, 24, 32, 40 and 48 (or Early Termination) to evaluate physical functioning. The scale has been developed specifically for patients with GNEM based on feedback received from affected individuals on the impact of the disease on their function. Items in the scale assess the subject's ability to independently perform various activities of living that involve self-care, mobility and use of the upper and lower extremities. The scale will be administered in an interview format by a trained clinician (preferably a licensed physical therapist) and scored after the testing. The physical therapists' role is a combination of observing subjects conducting activities and asking subjects questions to assess performance of these activities.

### **7.5.2.4 Sit-to-Stand Test**

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

### **7.5.2.5 Weighted Arm Lift Test**

Upper extremity function will be assessed using a weighted arm lift test. The weighted arm lift test ([Agarwal et al. 2006](#)) will be administered at the Screening Visit for training purposes, then at each subsequent scheduled visit through Week 48 (or Early Termination). The subject will be asked to sit in a chair holding a 1 kg barbell with the shoulder adducted, the elbow in full flexion, and the forearm in supination. On command, the subject will be asked to lift the arm above the head until the elbow is fully extended, then to lower the arm back to the starting position. The subject will be asked to repeat the action at a comfortable pace according to their own rhythm for the 30 second duration of the test. The test will be performed bilaterally and the final score will be the mean of the total number of completed



repetitions from both arms. The number of times the subject can raise the 1 kg weight above the head in the 30-second test period will be recorded as a secondary endpoint.

#### **7.5.2.6 Six Minute Walk Test**

The 6MWT will be administered at the Screening visit to determine eligibility. The 6MWT will be administered once per test day at each subsequent scheduled study visit through Week 48 (or Early Termination). Refer to the Study Reference Manual for detailed instructions on conducting the 6MWT.

The 6MWT will be conducted based on American Thoracic Society guidelines ([ATS/ERS 2002](#)). The course length has been modified to 20 meters to allow consistency across testing sites and the BORG scale will not be utilized. Subjects will be instructed to walk the length of a pre-measured course for 6 consecutive minutes. If applicable, the use of any AFOs in the performance of the 6MWT will be noted. Devices other than AFOs may not be used during the baseline assessment; if a subject's disease progresses substantially during the study and there are safety concerns with performing the 6MWT, then additional devices may be used and must be noted on the CRF. The total distance walked (meters) following the six minute period will be recorded as a secondary endpoint. As an additional secondary endpoint, the percent predicted distance walked (for age and gender) will also be determined based on published normative data ([Gibbons et al. 2001](#)).

#### **7.5.2.7 Individual Neuromuscular Quality of Life Questionnaire**

The INQoL ([Vincent et al. 2007](#)), a tertiary endpoint, is an individualized self-report measure of health-related quality of life designed specifically for adults with muscle disease. The INQoL will be administered at the Baseline Visit and Weeks 8, 16, 24, 32, 40, and 48 (or Early Termination). The INQoL will be presented to the subject in paper format for completion prior to the administration of the performance tests. The INQoL is a 45-item measure consisting of ten subscales; four measure the impact of muscle disease symptoms, including weakness, locking (seizing), pain and fatigue of muscles. Five additional subscales evaluate the degree of symptom impact on particular areas of life, including activities, independence, social, emotional, and body image. The final domain assesses perceived and expected treatment effects and will not be administered due to the blinded nature of the study. All responses are given in a seven-point Likert scale, with higher scores indicating greater impact.

The INQoL will only be completed for subjects when a validated version of the scale is available in the subject's native language.

#### **7.5.2.8 Clinical Global Impression Scale**

The CGI (a tertiary endpoint) was developed for use in National Institute of Mental Health-sponsored clinical trials to provide a brief, stand-alone assessment of the clinician's view of the patient's global functioning prior to and after initiating a study medication ([Guy 1976](#)).

The CGI provides an overall clinician-determined summary measure that takes into account all available information, including knowledge of the patient's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the patient's ability to function.

The Investigator will perform the CGI-Severity scale (CGI-S) at the Baseline Visit to rate the severity of a subject's condition on a 7-point scale ranging from 1 (normal, not at all ill) to 7 (among the most extremely ill subjects). The Investigator will also identify 3 target areas of improvement with the subject, which will be recorded in the source documents. To generate the targets, an open-ended question should be asked, such as "If this program of treatment works for you, what things do you hope you will be doing better?"

At Weeks 24 and 48 (or Early Termination), the Investigator will administer the CGI-Improvement (CGI-I) scale to assess the subject's overall improvement in the 3 target areas recorded at the Baseline Visit, using a 7 point scale ranging from 1 (very much improved) to 7 (very much worse). The CGI-S and CGI-I should be completed by a clinician experienced in the evaluation of patients with GNEM.

#### **7.5.2.9 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 (a tertiary endpoint) will be measured as indicated in the Schedule of Events ([Table 2.1](#)) to assess the degree of reduction associated with treatment.

#### **7.5.3 Drug Concentration Measurements**

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

The free, total, and bound urine SA levels (corrected for creatinine) will be measured. At the Baseline, and Week 16, 32, and 48 (or Early Termination) visits, first-morning void urine will be collected (pre-dose) to assess trough levels; the volume obtained will be recorded.

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

#### **7.5.4 Urine Testing for ManNAc**

An aliquot from the urine sample provided for the standard urinalysis testing will be analyzed for the presence of ManNAc at Screening, Baseline, and Week 16, 32, and 48 (or Early Termination) visits to detect noncompliance with prohibited medication restrictions.

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



### **7.5.5 Safety Measures & General Assessments**

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

#### **7.5.5.1 Medical History**

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

#### **7.5.5.2 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. Height should be measured in inches or centimeters without shoes with the subject standing on a flat surface. A calibrated scale must be used for all weight measurements. Weight should be measured in pounds or kilograms without shoes.

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

#### **7.5.5.3 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).

#### **7.5.5.4 Physical Examination**

Complete physical examinations will be performed at Baseline, and the Week 24 and 48 study visits (or Early Termination). Physical examinations will include assessments

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

#### **7.5.5.5 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 before any additional assessments are completed.

#### **7.5.5.6 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 7.5.5.6.1. Clinical laboratory testing will be performed at every visit. Blood and urine samples will be collected prior to administration of study drug; fasting is not required. Refer to the Laboratory Manual for additional details.

**Table 7.5.5.6.1: Clinical Laboratory Assessments for Safety**

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

<sup>1</sup> Also designated as PD variable (Section 7.5.2.9)

<sup>2</sup> Relevant to Drug Concentration Measurements (Section 7.5.3)

<sup>3</sup> To screen for use of prohibited medications (Section 7.4.6.1)

If urinalysis detects protein, leukocyte esterase, blood or nitrite, microscopic examination will be conducted. The microscopic examination will consist of White Blood Cell (WBC), Red Blood Cell (RBC), Epithelial Cells: Squamous, Epithelial Cells: Transitional, Epithelial Cells: Renal Tubular, Hyaline Casts, WBC Casts, RBC Casts, Waxy Casts, Granular Casts, Calcium Oxalate Crystals, Uric Acid Crystals, Triphosphate Crystals, Yeast, Bacteria, Amorphous Urates, and Amorphous Phosphates.

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

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

### 7.5.5.6.1 Volume of Blood to Be Drawn from Each Subject

During this study, it is expected that approximately 16 mL of blood will be drawn from each subject, at each required time point, regardless of gender or age. The amount of blood required for each sample type is presented in Table 7.5.5.6.1.1. 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 7.5.5.6.1.1: Volume of Blood to Be Drawn From Each Subject**

Assessment		Sample Volume (mL)	Number of Samples	Total Volume (mL)
Safety	Chemistry <sup>1</sup>	7.5	8	60
	Hematology	3	8	24
PK	Sialic Acid	5	7	35
Total mL through study completion				119

<sup>1</sup> Includes CK, an efficacy variable

### 7.5.5.7 Pregnancy Testing

Female subjects of childbearing potential with a positive pregnancy test at Screening will not be enrolled in the study. Female subjects will have urine pregnancy tests at the Baseline visit, at 16-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 3 months after last dose of study drug. Examples of highly effective methods of contraception include oral hormonal contraceptives, patch hormonal contraceptives, vaginal ring, intrauterine device, physical double-barrier methods, surgical hysterectomy, vasectomy, tubal ligation or true abstinence (when this is in line with the preferred and usual lifestyle of the subject), which means not having sex for the duration specified above because the subject chooses not to.

#### **7.5.5.7.1 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. Refer to the Study Reference Manual for details on the reporting procedures to follow in the event of pregnancy.

#### **7.5.5.8 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.

#### **7.5.5.9 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 7.4.6.

#### **7.5.5.10 Adverse Events**

All AEs will be recorded from the time the subject signs the informed consent until 30 days after the last dose of study drug, or, if applicable, until the date the subjects signs the informed consent for the open-label 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.

### **7.5.6 Appropriateness of Measures**

The efficacy parameters to be evaluated in this study include clinical changes in muscle strength, subject mobility and function. The clinical assessments in the study employ standard performance measures used in other neuromuscular diseases and conditions that cause muscle weakness and impaired function. Based on results from Phase 2 studies 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](#)). An interview-based measure designed to evaluate ability in GNEM patients (GNEM-FAS) will be administered in this study to support the clinical meaningfulness of changes in muscle strength. In addition, walking ability will be assessed using the 6MWT test, a test of endurance commonly used in clinical trials for various indications that has served as the basis for many product approvals.

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

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

### **7.6 Statistical Methods and Determination of Sample Size**

The completeness of the data affects the integrity and accuracy of the final study analysis. Therefore, every effort will be made to ensure complete, accurate and timely data collection, and to avoid missing data. The procedures for handling missing, unused, or spurious data, along with the detailed method for analysis of each endpoint 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

Based on the results of the Phase 2 study (UX001-CL201), approximately 80 subjects will be randomized in this Phase 3 study. This sample size will provide 90% power to detect a difference of about 5 kg in the UEC score change from baseline between the SA-ER treatment and the placebo groups, assuming a standard deviation of 6, and a two-sided alpha of 0.05.

### 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

**Primary Analysis Set:** The primary efficacy set will include all randomized subjects with a baseline measurement and at least one post-baseline measurement. Each subject will be included in the treatment group assigned at randomization, regardless of the treatment received. This set will be used for the primary analyses of all efficacy endpoints.

**Safety Analysis Set:** The safety analysis set consists of all randomized 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 or urine 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, sit-to-stand test, weighted arm lift test, and 6MWT 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 primary analysis set and will be stratified by gender. GEE analysis will be performed to compare the two treatment groups with respect to the changes from baseline of primary endpoint, secondary endpoints, and all tertiary efficacy endpoints. Baseline, gender, and geographic region will be included as covariates in the model. In general, randomly missing data for an individual subject will be treated as missing. The GEE method handles these cases appropriately. If a subject drops out following a decline in function, regardless of whether that is the reason listed for withdrawal, then it will be assumed that missing data are not missing at random and a single imputation rule will be used. 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. All analyses and tabulations will be performed using SAS<sup>®</sup> or SPLUS. 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.

#### **7.6.4.1 Primary Efficacy Endpoint and Analysis**

The primary clinical efficacy analysis will be the change from baseline in UEC score for the SA-ER group compared with placebo based on bilateral strength recorded in the following muscle groups using a dynamometer: gross grip, shoulder abductors, elbow flexors, and elbow extensors. The UEC is derived from the sum of the muscle groups. Each muscle group value will represent the average of the right and left total values (measured in kg).

The comparison of the two treatment groups will be based on the change from baseline in mean UEC score between SA-ER and placebo using GEE repeated measures analysis with baseline, gender, and geographic region as covariates. Region is considered as a covariate to account for the heterogeneity of the disease observed in some European countries and Israel relative to North American patients.

For missing assessments for an individual subject, these data would remain as missing or will be imputed based on the rules provided in the SAP. For those subjects who are in the study for some period of time but decline in function and leave the study, regardless of whether that is the reason listed for withdrawal, the GEE method might not adequately cover the projected decline for these subjects and may not be appropriately conservative. In such cases a single imputation method will be used to estimate the change in strength over the remaining time of the study using the existing subject's data and these imputed values will be used for the GEE analysis.

Details on primary endpoint analysis will be fully delineated in the SAP.

#### **7.6.4.2 Secondary Endpoints and Analyses**

Analyses of secondary efficacy endpoints will follow the same methods as the primary analyses of the primary endpoint, where data are available. Additional details on the analysis of secondary endpoints will be described in the SAP.

##### **7.6.4.2.1 Key Secondary Endpoints**

The key secondary clinical efficacy analyses will assess the change from baseline for the SA-ER group compared with the placebo group using GEE for the following variables:

- LEC score based on a sum of the mean bilateral strength recorded in the following muscle groups: knee flexors, hip flexors, hip extensors, hip abductors and hip adductors



- Muscle strength in the knee extensors: bilateral total force (measured in kg)
- GNEM-FAS mobility domain score

Hochberg's adjustment for multiplicity ([Hochberg 1988](#)) will be used for the key secondary endpoints, specifically LEC score, knee extensor strength, and GNEM-FAS mobility domain score.

#### **7.6.4.2.2 Other Secondary Endpoints**

The analysis of other secondary endpoints will assess the change from baseline for the SA-ER group compared to the placebo group using GEE for the following variables:

- GNEM-FAS upper extremity domain score
- Sit-to-stand score calculated as the number of times a subject can rise from a sitting to a standing position in a 30-second period
- Weighted arm lift score calculated as the number of times a subject can raise a 1 kg weight overhead in a 30-second period
- Walking ability as measured by the 6MWT, which will be reported as distance in meters and percent predicted based on normative data for age and gender.

#### **7.6.4.3 Tertiary Endpoints and Analysis**

Analyses of tertiary endpoints will follow the same methods as the primary analyses of the primary endpoint, where data are available. The tertiary clinical efficacy analyses will assess the change from baseline for the SA-ER group compared to the placebo group using GEE for the following endpoints:

- UEC score based on percent predicted bilateral strength recorded in the upper extremity muscle groups
- LEC score based on percent predicted bilateral strength recorded in the upper extremity muscle groups
- Muscle strength (total force in kg) for each individual muscle group comprising the UEC and LEC
- Percent predicted muscle strength for each individual muscle group comprising the UEC and LEC using published normative data adjusted for age, gender, and weight
- Percent of predicted muscle strength in the knee extensors using published normative data adjusted for age, gender, and weight
- GNEM-FAS total score
- GNEM-FAS self-care domain score

- Health-related quality of life as measured by the INQoL, which will be reported as subscale scores with higher scores associated with more significantly diminished quality of life
- CGI-I scores
- CK levels in serum
- Trough (pre-dose) SA levels in serum (free) and urine (free, total, and bound; corrected for creatinine)

Additional details on the analysis of tertiary endpoints will be described in the SAP.

### **7.6.5 Analyses of Drug Concentration Measurements**

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

### **7.6.6 Safety Analyses**

The safety analysis set will be used for the analyses of all safety endpoints (Section 7.6.3). Safety will be evaluated by the incidence, frequency and severity of AEs and SAEs, including clinically significant changes from study baseline to scheduled time points in:

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

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

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

statistics will be provided for study baseline and all subsequent post-treatment scheduled visits. Changes from study baseline to the post-treatment visits will also be provided.

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

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

### **7.6.7 Data Monitoring Committee**

An independent DMC with appropriate expertise in the conduct of clinical trials will act in an advisory capacity to monitor subject safety on a routine basis throughout the trial. A review of blinded safety data will be conducted by the DMC at least two times a year, with the first meeting scheduled once the first subject has been enrolled. Ad hoc meetings will be held if indicated based on observed events. The responsibilities of the DMC will be fully defined in a DMC charter.

## **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 15 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 15 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 15 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 the informed consent through 30 days following the last dose of study drug, or, if applicable, until the date the subject signs

the informed consent for the open-label extension study, UX001-CL302, whichever occurs sooner. In addition for those subjects choosing not to enroll in UX001-CL302, the Investigator should report any AE that occurs more than 30 days following the last dose of study drug that is believed to have a reasonable possibility of being associated with study drug.

AEs ongoing after the defined follow-up period stated in the paragraph above 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 through the defined follow-up period stated in Section 8.5.4.1 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 8.5.5.2.

### **8.5.5 Communication Plan**

#### **8.5.5.1 Review of Safety Data**

An independent DMC will act in an advisory capacity to monitor subject safety on a routine basis throughout the course of the study. The DMC will meet at least two times a year, or as needed, to review aggregate safety data and provide advice regarding the safety of subjects and the continuing scientific validity of the study. The DMC may also be asked to review SUSARs that represent changes in the nature or an increase in the frequency of events and may provide recommendations regarding continued subject participation.

Potential safety signals identified during the DMC reviews or any other process during the conduct of the study will be escalated to the appropriate internal Ultragenyx safety governing

bodies. Any action indicated by Ultragenyx safety governing bodies will be communicated accordingly to all stakeholders, e.g. Regulatory Authorities, ECs, IRBs, and Investigators.

### **8.5.5.2 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 SA, major safety findings) that may occur during the clinical trial that do not fall within the definition of a SUSAR but may affect the safety of subjects participating in the clinical trials, as required, in accordance with applicable laws and regulations. The reporting period for urgent safety issues is the period from the signing of the informed consent through the defined follow-up period stated in Section 8.5.4.1. 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 informed consent through the defined follow-up period stated in Section 8.5.4.1. Investigators are required to report any urgent safety measures to Ultragenyx within 24 hours.

Protocol Number: UX001-CL301 Amendment 5: 25 May 2017	
--	---

**8.5.7 Safety Contact Information**

Drug Safety	Medical Monitor
PrimeVigilance Fax: 1 (415) 930-4033 e-mail: ultragenyx@primevigilance.com	<div style="background-color: black; width: 100%; height: 15px; margin-bottom: 5px;"></div> <div style="background-color: black; width: 100%; height: 15px; margin-bottom: 5px;"></div> <div style="background-color: black; width: 100%; height: 15px;"></div>

**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.

## 9 REFERENCES

- Agarwal, S, and Kiely, PD. 2006. "Two simple, reliable and valid tests of proximal muscle function, and their application to the management of idiopathic inflammatory myositis." *Rheumatology (Oxford)* 45 (7):874-9.
- Aitkens, S, Lord, J, Bernauer, E, Fowler, WM, Jr., Lieberman, JS, and Berck, P. 1989. "Relationship of manual muscle testing to objective strength measurements." *Muscle Nerve* 12 (3):173-177.
- Argov, Z, Caraco, Y, H., L, Pestronk, A, Shieh, P, Skrinar, A, Mayhew, J, Marinisi, J, and Kakkis, E. 2014. Oral sialic acid extended release (SA-ER) stabilizes upper extremity muscle strength in human GNE myopathy: A Phase 2 study. In *66th American Academy of Neurology Annual Meeting. 26 April - 3 May 2014, Philadelphia, PA. [abstract]*.
- Argov, Z, and Yarom, R. 1984. "'Rimmed vacuole myopathy' sparing the quadriceps: A unique disorder in iranian jews." *J Neurol Sci.* 64 (1):33-43.
- ATS/ERS. 2002. "American Thoracic Society Statement: Guidelines for the six-minute walk test." *Am.J.Respir, Crit.Care Med* 166 (1):111-117.
- Bohannon, RW. 1997. "Reference values for extremity muscle strength obtained by hand-held dynamometry from adults aged 20 to 79 years." *Arch.Phys.Med.Rehabil.* 78 (1):26-32.
- Eisenberg, I, Avidan, N, Potikha, T, Hochner, H, Chen, M, Olender, T, Barash, M, Shemesh, M, Sadeh, M, Grabov-Nardini, G, Shmlevich, I, Friedmann, A, Karpati, G, Bradley, WG, Baumbach, L, Lancet, D, Asher, EB, Beckmann, JS, Argov, Z, and Mitrani-Rosenbaum, S. 2001. "The UDP-N-acetylglucosamine 2-epimerase/N-acetylmannosamine kinase gene is mutated in recessive hereditary inclusion body myopathy." *Nat.Genet.* 29 (1):83-87.
- Gibbons, WJ, Fruchter, N, Sloan, S, and Levy, RD. 2001. "Reference values for a multiple repetition 6-minute walk test in healthy adults older than 20 years." *J Cardiopulm.Rehabil.* 21 (2):87-93.
- Guy, W. 1976. "The Clinical Global Impression Scale." In *Handbook of Psychiatric Measures, 2008*, edited by A. John Rush Jr, M.B First and D Blacker, 90-92. Washington, DC: American Psychiatric Publishing, Inc.
- Hochberg, Y. 1988. "A sharper Bonferroni procedure for multiple tests of significance." *Biometrika* 75 (4):800-802.
- Huizing, M, and Krasnewich, DM. 2009. "Hereditary inclusion body myopathy: a decade of progress." *Biochim.Biophys.Acta* 1792 (9):881-887.
- Jay, CM, Levonyak, N, Nemunaitis, G, Maples, PB, and Nemunaitis, J. 2009. "Hereditary Inclusion Body Myopathy (HIBM2)." *Gene Regul.Syst.Bio* 3:181-190.

Malicdan, MC, Noguchi, S, Hayashi, YK, Nonaka, I, and Nishino, I. 2009. "Prophylactic treatment with sialic acid metabolites precludes the development of the myopathic phenotype in the DMRV-hIBM mouse model." *Nat.Med* 15 (6):690-695.

Malicdan, MC, Noguchi, S, and Nishino, I. 2008. "Recent advances in distal myopathy with rimmed vacuoles (DMRV) or hIBM: treatment perspectives." *Curr.Opin.Neurol* 21 (5):596-600.

Mathiowetz, V, Kashman, N, Volland, G, Weber, K, Dowe, M, and Rogers, S. 1985. "Grip and pinch strength: normative data for adults." *Arch Phys Med Rehabil* 66 (2):69-74.

Mizusawa, H, Kurisaki, H, Takatsu, M, Inoue, K, Mannen, T, Toyokura, Y, and Nakanishi, T. 1987. "Rimmed vacuolar distal myopathy: a clinical, electrophysiological, histopathological and computed tomographic study of seven cases." *J Neurol* 234 (3):129-136.

Nalini, A, Gayathri, N, and Dawn, R. 2010. "Distal myopathy with rimmed vacuoles: report on clinical characteristics in 23 cases." *Neurol India* 58 (2):235-241.

NIMS. 1996. "Muscular weakness assessment: use of normal isometric strength data. The National Isometric Muscle Strength (NIMS) Database Consortium." *Arch Phys Med Rehabil* 77 (12):1251-5.

Nonaka, I, Noguchi, S, and Nishino, I. 2005. "Distal myopathy with rimmed vacuoles and hereditary inclusion body myopathy." *Curr.Neurol.Neurosci.Rep.* 5 (1):61-65.

Nonaka, I, Sunohara, N, Ishiura, S, and Satoyoshi, E. 1981. "Familial distal myopathy with rimmed vacuole and lamellar (myeloid) body formation." *J Neurol Sci.* 51 (1):141-155.

Ozalevli, S, Ozden, A, Itil, O, and Akkoclu, A. 2007. "Comparison of the Sit-to-Stand Test with 6 min walk test in patients with chronic obstructive pulmonary disease." *Respir Med* 101 (2):286-93.

Peters, MJ, van Nes, SI, Vanhoutte, EK, Bakkers, M, van Doorn, PA, Merkies, IS, Faber, CG, and PeriNom, SSg. 2011. "Revised normative values for grip strength with the Jamar dynamometer." *J Peripher Nerv Syst* 16 (1):47-50.

Posner, K, Brown, GK, Stanley, B, Brent, DA, Yershova, KV, Oquendo, MA, Currier, GW, Melvin, GA, Greenhill, L, Shen, S, and Mann, JJ. 2011. "The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults." *Am J Psychiatry* 168 (12):1266-77.

Sadeh, M, Gadoth, N, Hadar, H, and Ben-David, E. 1993. "Vacuolar myopathy sparing the quadriceps." *Brain* 116 ( Pt 1):217-232.

Sisto, SA, and Dyson-Hudson, T. 2007. "Dynamometry testing in spinal cord injury." *J.Rehabil.Res.Dev.* 44 (1):123-136.

Sunohara, N, Nonaka, I, Kamei, N, and Satoyoshi, E. 1989. "Distal myopathy with rimmed vacuole formation. A follow-up study." *Brain* 112 ( Pt 1):65-83.

Vincent, KA, Carr, AJ, Walburn, J, Scott, DL, and Rose, MR. 2007. "Construction and validation of a quality of life questionnaire for neuromuscular disease (INQoL)." *Neurology* 68 (13):1051-7.