STATISTICAL ANALYSIS PLAN

Title	**Phase 3b Open-label Extension Study to Evaluate the Safety and Efficacy of Aceneuramic Acid Extended-Release (Ace-ER) Tablets in Patients with GNE Myopathy (GNEM) or Hereditary Inclusion Body Myopathy (HIBM)**
Protocol:	**UX001-CL302**
Protocol Version:	**Amendment 1 (17 June 2016)**
Investigational Product:	**Aceneuramic Acid Extended-Release (Ace-ER) Tablets**
Phase:	**3b**
Sponsor:	**Ultragenyx Pharmaceutical Inc.** **60 Leveroni Court** **Novato, CA, USA 94949**
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ABBREVIATIONS

6MWT	Six Minute Walk Test
Ace-ER	Aceneuramic Acid Extended-Release
AE	adverse event
ATC	Anatomical Therapeutic Chemical
CK	creatine kinase
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
DMC	data monitoring committee
DMRV	distal myopathy with rimmed vacuoles
ET	early termination
GEE	generalized estimating equation
GNE/MNK	glucosamine (UDP-N-acetyl)-2-epimerase/N-acetylmannosamine kinase
GNEM	GNE Myopathy
GNEM-FAS	GNE Myopathy Functional Activities Scale
HHD	hand held dynamometry
HIBM	hereditary inclusion body myopathy
INQoL	Individualized Neuromuscular Quality of Life Questionnaire
IP	investigational product
LEC	lower extremity composite
ManNAc	N-acetyl-D-mannosamine
MedDRA	Medical Dictionary for Regulatory Activities
MCS	mental component summary
CTCAE	Common Terminology Criteria for Adverse Events
PCS	physical component summary
PT	preferred term
qHS	at the time of sleep (i.e., at bedtime)
SA	sialic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan

SAS	Statistical Analysis System
SD	standard deviation
SF-36v2	Short Formc-36 Health Survey version 2
SOC	system organ Class
TEAE	treatment-emergent adverse event
TID	three times per day
UEC	upper extremity composite
US	United States

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within the UX001-CL302 original protocol dated 10 February 2016 and the UX001-CL302 Protocol Amendment 1 dated 17 June 2016. Should there be a difference between the SAP and the protocol with respect to analysis methods, the SAP will take precedence over the protocol.

2 STUDY OBJECTIVE(S)

The study objective is to evaluate the long-term safety and efficacy of Ace-ER treatment of GNE Myopathy subjects.

2.1 Overall Safety Objective(s)

Primary objective is to evaluate the long-term safety of 6 g/day Ace-ER treatment in subjects with GNE Myopathy.

2.2 Overall Efficacy Objective(s)

Secondary objective is to evaluate the long-term effect of 6 g/day Ace-ER treatment in subjects with GNE Myopathy.

3 STUDY DESIGN

This open-label extension study of will assess the long-term safety and efficacy of Ace-ER treatment over a period of 24 months. Approximately 180 subjects from the UX001-CL202, UX001-CL301, and UX001-CL203 studies will be eligible to enroll in the study.

Subjects will take 4 tablets (500 mg Ace-ER each for 2 g per dose) orally 3 times per day (TID). The dose should be taken with food (i.e. within 30 minutes after a meal or snack). Subjects being treated with 12 g/day Ace-ER in UX001-CL202 will be transitioned to 6 g/day Ace-ER dose in this protocol. Treatment will be administered for a total of 24 months. Study visits will occur every 8 weeks for 24 weeks and then every 6 months for subjects enrolling from UX001-CL202 or UX001-CL301. For subjects enrolling from UX001-CL203 studies, study visits will occur every 6 months. The schedule of assessments is shown in Appendix 10.4.

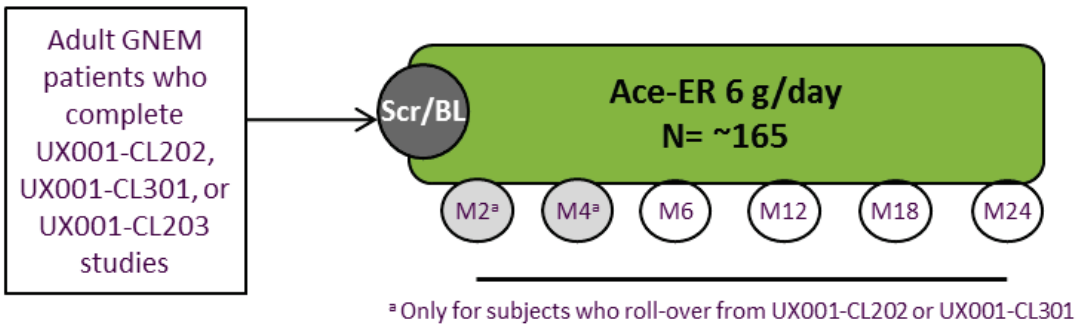
Safety will be evaluated by review of the incidence and frequency of AEs and SAEs and clinically significant changes in interval history, physical examination results, vital signs, clinical laboratory test results, the Columbia Suicide Severity Rating Scale (C-SSRS) (Posner et al. 2011), and concomitant medications.

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

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

A study schema demonstrating the enrolling patient populations and scheduled study visits is shown in Figure 3.1.

Figure 3.1: Study Schema



3.1 Study Population

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

Individuals who have ingested N-acetyl-D-mannosamine (ManNAc) or similar other SA-producing compounds during the 60 days prior to the Screening Visit will be excluded as it could confound interpretation of the results.

3.2 Dosage and Administration

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

Treatment will be administered for a total of 24 months (96 weeks).

3.3 Blinding and Randomization Methods

This is open-label extension study consists of one treatment arm. All subjects will be treated with Ace-ER 6 g/day. Randomization and blinding are not applicable.

3.4 Stratification Factors

No stratification factors are planned.

3.5 Sample Size Considerations

The current study is primarily designed to evaluate safety and the sample size is intended to provide the maximum amount of information regarding UX001 tolerability along with indicators of long-term safety and efficacy in this patient population.
Approximately 180 adult subjects with GNEM are expected to roll-over from UX001-CL202, UX001-CL301, and UX001-CL203 studies to participate in this extension study.

3.6 Interim Analysis

No interim analysis is planned for this study.

3.7 Data Monitoring Committee

No formal DMC is planned for this study in the protocol. Conduct of the study and safety of the patients will be monitored by Ultragenyx on a regular basis.

4 STUDY ENDPOINTS AND COVARIATES

All data are collected according to the schedule of assessments (Appendix 10.4).

Overall safety endpoints serve to evaluate the long-term safety of 6 g/day Ace-ER treatment in subjects with GNE Myopathy (primary objective).

Overall efficacy endpoints serve to evaluate the long-term effect of 6 g/day of Ace-ER treatment in subjects with GNEM.

4.1 Safety Endpoints

4.1.1 Primary Safety Endpoint

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

4.1.2 Other Safety Endpoints

Other safety endpoints include clinically significant changes from baseline to scheduled time points in the following:

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

Drug concentration endpoints will be evaluated for the following:

- Changes from baseline in free SA level in serum;
- Changes from baseline in urine SA level;
- Frequency and percentage of subjects with the presence of ManNac detected from urine testing.

4.2 Efficacy Endpoints

Efficacy evaluations will be based on the parent study (UX001-CL202, UX001-CL301, or UX001-CL203) from which the subjects enroll. Subjects enrolling from UX001-CL202 follow the same schedule of visits for the efficacy assessments as subjects who roll over from UX001-CL301. Subjects enrolling from UX001-CL203 follow a different schedule of visits.

For subjects enrolling from UX001-CL202 and UX001-CL301:

Primary Clinical Efficacy Endpoint:

- Changes from baseline in upper extremity composite score (UEC) based on bilateral strength recorded in the following muscle groups: gross grip, shoulder abductors, elbow flexors, and elbow extensors as measured by dynamometry. The UEC is derived from the sum of the average of the right and left total force values (measured in kg);

Secondary Clinical Efficacy Endpoints:

- Changes from baseline in the scores on the mobility domain of GNEM-FAS;
- Change from baseline in the scores on the upper extremity domain of GNEM-FAS;
- Changes from baseline in lower extremity composite score (LEC) based on bilateral strength recorded in the following muscle groups: knee flexors, hip flexors, hip extensors, hip abductors and hip adductors as measured by dynamometry. The LEC is derived from the sum of the average of the right and left total force values;
- Change from baseline in the number of stands in the Sit-to-Stand test;
- Changes from baseline in the number of lifts in 30 second weighted arm lift;
- Changes from baseline in meters walked in 6MWT and percent predicted distance based on normative data for age and gender;
- Changes from baseline in total force and percent predicted total force in the Knee Extensors. The percent predicted total force value will be determined based on reference equations adjusting for age, gender, height, and weight.

Tertiary Efficacy Endpoints:

- Changes from baseline in UEC and LEC percent predicted based on reference equations adjusting for age, gender, height, and weight;
- Changes from baseline in bilateral total force and percent predicted total force for each individual muscle group included in the UEC and LEC;
- Changes from baseline in the score on self-care domain on GNEM-FAS;
- Changes from baseline in the total score on GNEM-FAS;
- Change from baseline in in the total score from a 45-item self-report questionnaire (INQoL) 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;
- Changes from baseline in CK levels in serum to assess the degree of reduction of CK levels observed as a surrogate for muscle injury.

For subjects enrolling from UX001-CL203:

Primary Clinical Efficacy Endpoints:

- Changes from baseline in the mobility domain of GNEM-FAS Expanded Version;
- Changes from baseline in the upper extremity domain of GNEM-FAS Expanded Version;
- Changes from baseline in the self-care domain of GNEM-FAS Expanded Version;
- Changes from baseline in the total scores of GNEM-FAS Expanded Version;
- Changes from baseline in upper extremity muscle strength and percent predicted in the following muscle groups: grip, key pinch, shoulder abductors and wrist extensors as measured by HHD
- Changes from baseline in lower extremity muscle strength and percent predicted in the knee extensors as measured by HHD

Exploratory endpoints:

- Changes from baseline in 8 subscales and summary scores (PCS and MCS) in health-related quality of life as assessed by using Short Form Health Survey – 36 (SF-36v2);
- Changes from baseline in creatine kinase (CK) and serum aceneuramic acid.

Assessments, upon which efficacy endpoints are based on, are shown in Table 4.2.1. Detailed information on efficacy endpoints and visit schedules by study can be found in Appendix 10.1.

Table 4.2.1: Efficacy Assessments Performed by Parent Study

	CL202 and CL301	**CL203**
Assessment	Week 0, 8, 16, 24, 48, 72, 96	Week 0, 24, 48, 72, 96
Functional	HHD* 6MWT Sit-to-Stand Test Weighted Arm Lift Test GNEM FAS	HHD^ GNEM FAS expanded version
QoL Questionnaire	INQoL	SF-36 short form
Biomarker	CK Free serum SA Urine ManNAc	

* Measured by HHD, the Upper Extremity Composite (UEC) Score is based on gross grip, shoulder abductors, elbow flexors, and elbow extensors. The Lower Extremity Composite (LEC) Score is based on knee flexors, hip flexors, hip extensors, hip abductors, and hip adductors.
^ Measured by HHD, UEC is not defined in this study for analysis, since different muscle groups from the other two studies are measured. Lower extremity muscle strength of knee extensors is included.

5 DEFINITIONS

5.1 Baseline

Two baselines are defined for the statistical analysis variable derivations.

- **Current study baseline** is defined as the last observed value before the first dosing of the study drug for CL302.
- **Parent study baseline** is defined as the last observed value before the first dosing of the IP study drug from CL202, CL203, or CL301 depending on which study the subject was enrolled from.

Current study baseline is defined for all safety summaries and analyses.

Efficacy summaries and analyses will be performed upon the parent study baseline and the current study baseline as specified in Table 8.1.1.

5.2 Subgroup

The following subgroups are defined for this study:

- Gender (Male and Female)
- Age (above and below median)
- Ethnicity (small groups may be combined)
- Genetic Mutation
  - Genotype: Homozygote, Heterozygote, and Compound Heterozygote
  - Mutation type: Exon and Intron

Genetic mutation subgroup analysis will be done for the following primary efficacy endpoints: the changes from baseline in UEC score in subjects enrolled from CL301 and CL202; and the changes from baseline in lower extremity muscle strength of knee extensors in subjects enrolled from CL203.

Gender, age, and ethnicity subgroup summaries will be done to support the safety.

6 ANALYSIS SETS

Three analysis sets are defined for the study.

Full Analysis Set: The full analysis set will include all subjects with a CL302 baseline measurement and at least one post-baseline measurement in CL302. This set will be used for the efficacy analysis.

Safety Analysis Set: The safety analysis set consists of all subjects who receive at least one dose of study drug in CL302. This set will be used for safety analysis.

Sialic Acid Analysis Set: The SA analysis set will consist of all subjects with evaluable free serum SA levels in CL302.

7 DATA SCREENING AND ACCEPTANCE

7.1 General Principles

Data will be reviewed periodically. And any questionable data will be reported to the clinical data manager promptly for query and resolution.

7.2 Handling of Missing and Incomplete Data

Missing clinical outcome data can occur for multiple reasons, including missed subject visits and scales or measures with missing item scores. Missing and incomplete data will be identified through the data quality review plan for this study. Missing and incomplete data will be identified for investigation, and possible resolution, by Data Management prior to the study database lock or snapshot. Unless specified otherwise, only the observed data (not imputed data) will be presented in listings.

7.2.1 Missing Date of the Last Dose of Investigational Product

When the date of the last dose of investigational product is found missing for a subject, all efforts should be made to obtain the date from the Investigator. If after all efforts are made it is still missing, the last dosing visit date will be used as the last dose date.

7.2.2 Missing Efficacy Data

Details of missing HHD observations for individual muscle groups and individual questions for GNEM-FAS are provided in Appendix 10.2.

7.2.3 Missing Dates Information for Adverse Events and Concomitant Medications

The following conventions will be used to impute missing portions of dates for adverse events and concomitant medications. Note that the imputed values outlined here may not always provide the most conservative date. In those circumstances, the imputed value may be replaced by a date that will lead to a more conservative analysis.

Missing Start Dates

- If the day is unknown, then:
  - If the month and year match the first dose of investigational product start date month and year in this study, then impute the day of the first dose date.
  - Otherwise, assign the first day of the month.
- If the month is unknown, then:
  - If the year matches the year of the first dose of investigational product date in this study, then impute the month and day of the first dose date in this study.
  - Otherwise, assign ‘January’

- If the year is unknown, then the date will not be imputed and will be assigned a missing value.

If the imputed date is earlier than birth date, then birth date will be used

Missing Stop Dates

- If the day is unknown, then assign the last day of the month.
- If the month is unknown, then assign 'December.'
- If the year is unknown, then the date will not be imputed and will be assigned a missing value.

If the resulting end date is after the date of study completion / discontinuation/ data cutoff, set the imputed end date as the date of study completion / discontinuation/ data cutoff.

7.2.4 Missing Causal Relationship to Investigational Product for Adverse Events

If the causal relationship to the investigational product is missing for an AE that started on or after the date of the first dose of investigational product, a causality of "definitely related" will be assigned. The imputed values for causal relationship to investigational product will be used for the incidence summary; the values will be shown as missing in the data listings.

7.2.5 Visit Time Windows

There is no visit time window applied to handle the missing values for a scheduled visit. Nominal visits will be used for by-visit analyses. If an unscheduled visit has to be used, the principle of proximity will be applied.

7.3 Handling of Multiple Measurements in HHD

Each muscle strength is assessed three times in Hand Held Dynamometry (HHD) measurement. The highest value of the three will be used for summary and derivation of efficacy endpoints.

7.4 Testing/Validation Plan

Data will be reviewed by cross functional team periodically and issues will be addressed by clinical data management.

7.5 Software

SAS® software version 9.2 or higher will be used to perform statistical analyses unless otherwise specified.

8 STATISTICAL METHODS OF ANALYSES

8.1 General Principles

All statistical tests will be two-sided and a difference resulting in a p-value of less than or equal to 0.05 will be considered statistically significant. All p-values will be rounded to and displayed in four decimals. If a p-value less than 0.0001 occurs, it will be shown in the table as <0.0001.

Continuous variables will be summarized by number of subjects and mean, SD/SE, median, minimum, and maximum values. Categorical variables will be summarized by number and percentage. No imputation on missing data will be made, unless stated otherwise.

Data collected will be presented in listings. Data not subject to analysis according to this plan will not appear in any tables or graphs but will be included in the data listings.

Post-hoc exploratory analyses not identified in this SAP may be performed to further examine the study data. These analyses will be clearly identified as such in the final clinical study report. The SAP will not be amended for post-hoc or additional analyses identified after planned analyses are completed. Similarly, additional tables and figures may be defined to further evaluate study results and the SAP will not be amended to list them.

Efficacy analyses will be presented by the parent study as illustrated in Table 8.1.1: UX001-CL301, CL202 or CL203. Different efficacy endpoints at different scheduled time points were collected depending on which parent study the subjects were enrolled from.

Safety analyses will be presented by the parent studies and overall as illustrated in Table 8.1.1. Subjects enrolling from UX001-CL301 will be further examined by the treatment group assigned in the parent study: placebo, Ace-ER 6 g/day, and All.

Table 8.1.1 also provides the guidance for the treatment groups to be displayed for biomarker analyses as well as efficacy analyses and safety analyses, which have been described above. . Baseline used for the analyses are specified as well. Example table templates are provided in Appendix 10.6 for efficacy and safety.

Table 8.1.1: Analysis Presentation

Analysis Category	Analysis Set	Parent Study	Treatment Group	Baseline Applied
Week 96/ET efficacy analysis	Full Analysis Set	CL301	Placebo*	Parent Study Baseline
			Ace-ER 6 g/day	
			Placebo*	Current Study Baseline
			ACE-ER 6 g/day	
			All	
Week 96/ET efficacy analysis	Full Analysis Set	CL202	Ace-ER 6 g/day	Current Study Baseline
Week 96 /ET efficacy analysis	Full Analysis Set	CL203	Ace-ER 6 g/day	Parent Study Baseline
			Ace-ER 6 g/day	Current Study Baseline
Week 96/ET safety analysis	Safety Analysis Set	CL301	Placebo*	Current Study Baseline
			Ace-ER 6 g/day	
			All	
		CL202	Ace-ER 6 g/day	
		CL203		
		Total		
Week 96/ET analysis on biomarkers	Sialic Acid Analysis Set	CL301	Ace-ER 6 g/day	Current Study Baseline
		CL202		
		CL203		
		Total		

* This refers to the enrolled subjects who had received placebo treatment in parent study CL301.

8.2 Subject Disposition

All subjects screened for the study will be used for reporting of disposition.
Subject disposition summaries will include the number and percentage of subjects who are included in the safety, efficacy, and SA analysis sets; the number and percentage of subjects who received study drug treatment, completed the study or discontinued the study (with reasons) will be summarized by parent study and total.

8.3 Protocol Deviations

Major protocol deviations will be summarized. All protocol deviations will be listed.

8.4 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively for the full analysis set.

- Gender
- Age
- Age at start of parent study
- Race
- Ethnicity
- Height (cm)
- Weight (kg)
- Genotype: Homozygote, Heterozygote, and Compound Heterozygote
- Mutation type: Exon and Intron

8.5 Investigational Product Administration

8.5.1 Extent of Exposure

The total number of doses administered, the total dose administered, and the total treatment duration will be summarized for the Safety Analysis Set. The calculation will be based on the current study baseline unless otherwise specified.

Study medication dispensing and treatment compliance will also be listed.

8.5.2 Measurement of Treatment Compliance

Dosing compliance for a CL302 study period is defined as:

Actual total dosage taken during CL302 / Planned dosage for CL302 * 100%.

Descriptive statistics will be reported for compliance on the Safety Analysis Set.

8.6 Efficacy Analysis

Efficacy analyses will use generalized estimating equation (GEE) (Hanley et al. 2003) to evaluate trends over time with respect to the changes from baseline for all continuous efficacy endpoints. Baseline will be included as a covariate in the model. GEE will be the primary analysis method for all repeated measures endpoints. The statistical analyses will be reported in summary tables, figures, and data listings. Statistical tests will be 2-sided at the alpha=0.05 significance level.

Efficacy analysis will be based on the full analysis set.

Additional efficacy analyses may be performed for subjects enrolled in CL301 by incorporating data from both the parent study and the current study to compare the placebo versus UX001 treatment groups using the methodology described in (Hu et al. 2007). Such analyses examine the extended treatment effect of UX001 on the placebo subjects who now are taking UX001 in the extension study.

Parent study baseline will be used to evaluate the long-term study drug effect from the parent study drug administration, except for subjects enrolling from CL202.

Current study baseline will be used to evaluate the continuous long-term study drug effect going on after the parent study.

8.7 Safety Analysis

The safety analysis will be performed on the safety analysis set. Descriptive statistics will be provided for safety reporting by parent study and overall.

8.7.1 Adverse Events

All AEs recorded from the time the subject signs the informed consent through the safety follow-up will be coded using the Medical Dictionary for Regulatory Activities (MedDRA version 17.1 or beyond).

The following AEs were collected:

- All AEs;
- All SAEs;
- Treatment-related AEs;
- Treatment-related SAEs;
- AEs leading to the discontinuation of study drug or discontinuation of study;
- Deaths.

The number and proportion of subjects with any treatment-emergent adverse events (TEAEs) (defined generally as any AE started on or after the first dose of study drug) will be summarized by System Organ Class (SOC), Preferred Term (PT), severity, grade, outcome and relationship to treatment for the following types of AEs. Additional summaries of subject incidence (by preferred term) will also be provided.

An AE continued from the parent study would be excluded since they were summarized in the parent study. However, if an AE continued from the parent study and the severity changed to worse will be considered as a TEAE and be summarized.

The severity of AEs will be based on Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03. If an AE cannot be graded based on CTCAE, the investigator will assign a severity based on 1 = mild, 2 = moderate, 3 = severe, 4 = life threatening, and 5 = Death.

For those AEs that occurred more than once during the study, the maximum severity or highest grade will be used to summarize the subject incidence.

Detailed listings for all AEs, serious AEs, AEs leading to the discontinuation of study, and death will also be provided.

Subgroup analyses by gender, age (above and below median), and ethnicity (small group may be combined) will be performed to support the safety in GNEM patients.

8.7.1.1 Adverse Events to Monitor

Adverse events to be monitored are included in Appendix 10.5 by MedDRA preferred terms in categories of gastrointestinal AEs and liver-related investigations.

Tables summarizing patient incidents for the monitored adverse events will be generated.

8.7.2 Concomitant Medication

The number and percent of concomitant medications in CL302 will be summarized by ATC class and preferred term (per WHO-drug dictionary) in the safety analysis set.

If a subject took a specific medication multiple times or took multiple medications within a specific therapeutic class, that subject will be counted only once for the coded drug name or therapeutic class.

8.7.3 Clinical Laboratory Parameters

Descriptive statistics for clinical laboratory values and changes from the CL302 baseline values at each visit will be presented. The number and percentage of abnormalities for each lab parameter at each assessment time point will be reported.

8.7.4 Vital Signs

Descriptive statistics for vital signs including blood pressures, respiration rate, and heart rate and changes from CL302 baseline values at each scheduled visit and at the end of study will be presented. All results of vital signs will be listed.

8.7.5 Physical and Neurological Exams

A complete physical examination including neurological exam is performed at CL302 baseline. At post-baseline visit, a subset of physical examination (brief exam including

general appearance, cardiovascular exam, and respiratory exam) is conducted. The number and percentage of abnormal findings will be summarized for the complete physical exam. The number and percentage of deficit findings will be summarized for the neurological exam. The number and percentage of abnormal findings for the brief exam will be summarized for post-baseline visits in a similar fashion.

8.7.6 Interval History

The Interval history in CL302 will be summarized for number and percentage of patients who reported changes at each visit from the last visit.

8.7.7 Suicidal Ideation

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 and will be administered at each visit. Any 'Yes' response from C-SSRS will be listed.

8.7.8 Pregnancy Test

Pregnancy test will be conducted at the scheduled study visit and the results will be provided in a listing.

9 REFERENCES

Bohannon, RW. 1997a. "Comfortable and maximum walking speed of adults aged 20-79 years: reference values and determinants." *Age Ageing* 26 (1):15-9.

Bohannon, RW. 1997b. "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.

Hanley, JA, Negassa, A, Edwardes, MD, and Forrester, JE. 2003. "Statistical analysis of correlated data using generalized estimating equations: an orientation." *Am J Epidemiol* 157 (4):364-75.

Hu, Z, and Follmann, D. 2007. "Statistical methods for active extension trials." *Stat Med* 26 (12):2433-48.

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.

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.

Stoll, T, Huber, E, Seifert, B, Michel, BA, and Stucki, G. 2000. "Maximal isometric muscle strength: normative values and gender-specific relation to age." *Clin Rheumatol* 19 (2):105-13.

Visser, J, Mans, E, de Visser, M, van den Berg-Vos, RM, Franssen, H, de Jong, JM, van den Berg, LH, Wokke, JH, and de Haan, RJ. 2003. "Comparison of maximal voluntary isometric contraction and hand-held dynamometry in measuring muscle strength of patients with progressive lower motor neuron syndrome." *Neuromuscul Disord* 13 (9):744-50.

10 APPENDICES

10.1 Summary of Efficacy Endpoints and Analyses

Test / Instrument	Endpoint	Type of analysis	Time points for Assessment	Statistical approach at week 96/ET analysis
Subjects enrolling from UX001-202 and UX001-301				
Physical therapy – Hand-held Dynamometry (HHD)	The changes from baseline in Upper Extremity Composite (UEC) Score based on bilateral strength recorded in the following muscle groups: gross grip, shoulder abductors, elbow flexors, and elbow extensors	Primary analysis	Weeks 8, 16, 24, 48, 72, and 96	GEE Model
GNEM Functional Activities Scale (GNEM-FAS)	Changes from baseline on Upper Extremity Domain score Changes on Mobility Domain score	Secondary efficacy analysis	Weeks 8, 16, 24, 48, 72, and 96	GEE Model
Physical therapy – Hand-held Dynamometry (HHD)	Changes from baseline in lower extremity composite score (LEC) based on bilateral strength recorded in the following muscle groups: knee flexors, hip flexors, hip extensors, hip abductors and hip adductors. Changes from baseline in total force and percent predicted total force in the Knee Extensors.	Secondary efficacy analysis	Weeks 8, 16, 24, 48, 72, and 96	GEE Model
Sit to Stand	Change from baseline in the number of stands in the Sit-to-Stand test	Secondary efficacy analysis	Weeks 8, 16, 24, 48, 72, and 96	GEE Model
Weighed Arm Lift Test	Changes from baseline in the number of lifts in 30 second weighted arm lift tests	Secondary efficacy analysis	Weeks 8, 16, 24, 48, 72, and 96	GEE Model
6-Minute Walk Test	Changes from baseline in meters walked in 6MWT and percent predicted	Secondary efficacy analysis	Weeks 8, 16, 24, 48, 72, and 96	GEE Model

Test / Instrument	Endpoint	Type of analysis	Time points for Assessment	Statistical approach at week 96/ET analysis
Physical therapy – Hand-held Dynamometry (HHD)	Changes from baseline in UEC and LEC percent predicted based on reference equations adjusting for age, gender, height, and weight.	Tertiary efficacy analysis	Weeks 8, 16, 24, 48, 72, and 96	Summary statistics
	Changes from baseline in bilateral total force and percent predicted total force for each individual muscle group included in the UEC and LEC.			Summary statistics
GNEM Functional Activities Scale (GNEM-FAS)	Changes from baseline on the total score on the GNEM-FAS	Tertiary efficacy analysis	Weeks 8, 16, 24, 48, 72, and 96	Summary statistics
	Changes from baseline on the Self-Care Domain Score on the GNEM-FAS			
Individual Neuromuscular Quality of Life Questionnaire (INQoL) (Not including CL202 subjects)	Changes from baseline on the total score on a 45-item self-report questionnaire on the impact of key muscle disease symptoms on the ability to perform basic activities of daily living, functional independence, relationships and overall well-being	Tertiary efficacy analysis	Weeks 8, 16, 24, 48, 72, and 96	Summary statistics
Creatine Kinase (CK)	Changes from baseline in CK levels in serum to assess the degree of reduction of CK levels observed as a surrogate for muscle injury	Tertiary efficacy analysis	Weeks 8, 16, 24, 48, 72, and 96	Summary statistics
Subjects enrolling from UX001-203				
GNEM Functional Activities Scale (GNEM-FAS) Expanded Version	Changes from baseline in the total scores	Primary efficacy analysis	Weeks 24, 48, 72, and 96	GEE Model
	Changes from baseline in the mobility domain			
	Changes from baseline in the upper extremity domain			
	Changes from baseline in the self-care domain			

Test / Instrument	Endpoint	Type of analysis	Time points for Assessment	Statistical approach at week 96/ET analysis
Physical therapy – Hand-held Dynamometry (HHD)	Changes from baseline in upper extremity muscle strength and percent predicted in the following muscle groups: grip, key pinch, shoulder abductors and wrist extensors	Primary efficacy analysis	Weeks 24, 48, 72, and 96	GEE Model
	Changes from baseline in lower extremity muscle strength and percent predicted in the knee extensors			
Short Form Health Survey – 36 (SF-36v2)	Changes from baseline in 8 subscales and summary scores (PCS and MCS) in SF-36v2	Exploratory efficacy analysis	Weeks 24, 48, 72, and 96	Summary statistics
Biomarker	Changes from baseline in serum biomarkers: creatine kinase (CK), serum aceneuramic acid	Exploratory efficacy analysis	Weeks 24, 48, 72, and 96	Summary statistics

10.2 Missing Observation in Hand Held Dynamometry and GNEM-FAS

Imputation rules outlined in this section for dynamometry are defined below and are based on the distinct pattern of muscle weakness associated with GNE Myopathy and the features of the dynamometers used in this study. The most common cause of missing data is muscle weakness severe enough to prevent the subject from registering the minimum amount of force against the dynamometer required to obtain a measurement during a maximum voluntary isometric contraction maneuver. In those cases, the value is imputed to 0, and preserves the ability to calculate the UEC and LEC scores. There are some scenarios in which non-random missing HHD data values result in missing UEC and LEC values. When strength in a particular muscle group exceeds the resistance that can be applied by the administrator, a reliable value cannot be obtained from the dynamometer. This is a recognized limitation of a hand-held device (Visser et al. 2003). In GNE Myopathy, the only muscle group at risk for this scenario is the knee extensors, due to the relative sparing of the quadriceps. All other non-random missing HHD data are related to the clinical condition of the subject at the time of the testing where a test may not be administered due to pain, injury, contracture or another extenuating circumstance that could cause discomfort to the subject. The proposed plan for the handling of this data is intended to provide the most accurate estimate of muscle strength and physical function possible based on knowledge of the disease and the outcome measures obtained during the conduct of previous studies.

Missing observations in HHD for individual muscle group will be imputed based on reason for missing and if the muscle strength measurement is missing on both sides or one side. The table below provides a summary of the imputation rule followed by detailed descriptions.

Instrument	Missing Reason	Imputation
HHD missing *BOTH* sides	Too Weak	0
	Too Strong	NA , UE/LE composite not computed
	Pain	NA , UE/LE composite not computed
	Injury	NA , UE/LE composite not computed
	Contracture	NA , UE/LE composite not computed
	Other	NA , UE/LE composite not computed
HHD missing *ONE* side	Too Weak	0
	All other reasons	The value from the other side that was measured

Missing Reason = Weakness

A value of 0 should be imputed for a W.

- If both sides are W, a value of 0 is assigned to each side and the muscle group IS counted as part of the UE or LE composite.
- If one side is W, a value of 0 is assigned to that side and the 0 is averaged with the value from the other side. The muscle group IS counted as part of the UE of LE composite.

Missing Reason = Contracture

A value of 0 should NOT be imputed for a C. A C is missing data because the test was not performed due to the contracture.

- If both sides are C (which would be rare), then the data for this muscle group is missing and the UE or LE composite will be set to missing.
- If one side is C, then the data is missing from this side and the value from the other side should be used to reflect the total strength for this muscle group. The muscle group IS counted as part of the UE or LE composite.

Missing Reason = Pain

A value of 0 should NOT be imputed for a P. A P is missing data because the test was not performed due to pain.

- If both sides are P, then the data for this muscle group is missing and the UE or LE composite will be set to missing.
- If one side is P, then the data is missing from this side and the value from the other side should be used to reflect the total strength for this muscle group. The muscle group IS counted as part of the UE or LE composite.

Missing Reason = Injury

A value of 0 should NOT be imputed for an I. An I is missing data because the test was not performed due to pain.

- If both sides are I, then the data for this muscle group is missing and the UE or LE composite will be set to missing.
- If one side is I, then the data is missing from this side and the value from the other side should be used to reflect the total strength for this muscle group. The muscle group IS counted as part of the UE or LE composite.

Missing Reason = Too Strong

An S indicates that the test was attempted but that the subject overpowered the administrator and a valid value could not be obtained.

- If both sides are S, then the data for this muscle group is missing and the UE or LE composite will be set to missing.
- If one side is S, then the data is missing from this side and the value from the other side should be used to reflect the total strength for this muscle group. The muscle group IS counted as part of the UE or LE composite.

Missing Reason = OTHER

No value should be imputed if there is an O.

- If both sides are O, then the data for this muscle group is missing and the UE or LE composite will be set to missing.
- If one side is O, then the data is missing from this side and the value from the other side should be used to reflect the total strength for this muscle group. The muscle group IS counted as part of the UE or LE composite.

When an individual question is missing in GNEM-FAS. The average score is calculated for the domain and then multiplied by the number of questions in the domain:

Mobility Subscale Score = 10 x Sum(Available Items) / Number of Available Items

Upper Extremity Subscale Score = 8 x Sum(Available Items) / Number of Available Items

Self-Care Subscale Score = 7 x Sum(Available Items) / Number of Available Items

If a domain has more than 50% (inclusive) items missing (≥5 for Mobility, ≥4 for Upper Extremity, ≥3 for Self-Care), the domain score will not be calculated. The Total FAS core will only be calculated if all three domain scores are avaialble.

10.3 Computation Formula for Derived HHD Variables

Individual Muscle Strength Average Score = (left-side measurement + right-side measurement) / 2

UE Composite Score = sum(Individual Muscle Strength Average Score for muscle group gross grip, shoulder abductors, elbow flexors and elbow extensors)

LE Composite Score = sum(Individual Muscle Strength Average Score for muscle group knee flexors, hip flexors, hip extensors, hip abductors and hip adductors)

Predicted Normal for Individual Muscle Strength Average Score = (left-side predicted normal + right-side predicted normal) / 2

Predicted Normal for UE Composite Score = sum(Predicted Normal for Individual Muscle Strength Average Score for muscle group gross grip, shoulder abductors, elbow flexors and elbow extensors)

Predicted Normal for LE Composite Score = sum(Predicted Normal for Individual Muscle Strength Average Score for muscle group hip flexors, hip extensors, hip adductors and knee flexors)

% of predicted normal HHD values = (Observed strength value/ Predicted normal strength value) *100%.

Predicted normal HHD values can be derived using the regression equations outlined in Appendix 10.3.1.

10.3.1 Predicted Normal HHD Muscle Strength

Muscle Strength

Note: Many of the HHD derived variables detailed below rely on regression equations that have predictor variables in units different than what is found in the analysis datasets. Care will be taken to convert dataset variables to the correct units before they are entered into the prediction equation. The resulting predicted value will then, in turn, be converted to the appropriate unit for analysis.

Hand-Held Dynamometry

Shoulder abduction and hip abduction

Regression Equations and Multiple Correlations of Sex, Age, and Weight with Muscle Strength

Muscle Action	Side	Equation*	R	R^2
Shoulder Abduction	Nondominant	165.16 – 74.9S – .910A + .126W	.843	.710
	Dominant	178.90 – 77.1S – 1.128A + .134W	.843	.710
Hip Abduction	Nondominant	203.32 – 73.3S – 1.247A + .192W	.794	.630
	Dominant	195.24 – 62.4S – 1.184A + .198W	.764	.584

(Bohannon 1997b)
*Muscle strength results in Newtons (N). S, sex (male=0, female=1); A, age (years); W, weight (Newtons).

Note: Age and weight values collected at the Baseline visit will be used for the calculation of predicted values for shoulder abduction and hip abduction for all study time points.

Hip adduction

Muscle Action	Gender	Side	Age (years)	Equation
Hip Adduction	Female	Left	$\leq$ 55	19.1 – 0.30*(age -55)
	Female	Right	$\leq$ 55	19.5 – 0.00*(age -55)
	Female	Left	> 55	19.1 – 0.212*(age -55)
	Female	Right	> 55	19.5 – 0.245*(age - 55)
Hip Adduction	Male	Left	$\leq$ 49	31.8 + 0.044*(age – 49)
	Male	Right	$\leq$ 49	31.6 - 0.082*(age – 49)
	Male	Left	> 49	31.8 - 0.280*(age – 49)
	Male	Right	> 49	31.6 - 0.206*(age – 49)

(Stoll et al. 2000)
Median strength results in kiloponds (kp) also known as kilogram-force (kgf)

Note: The age category that applies for a subject at the Baseline visit will be used for the calculation of hip adduction predicted values for all study time points.

Elbow flexion, elbow extension, hip flexion, hip extension, knee flexion, knee extension

Regression Equations for Strength Prediction

Muscle Action	Equation
Right Elbow Flexion	- (age * 0.13) + (gender * 11.24) + ((weight/height^2) * 0.07) + 22.78
Left Elbow Flexion	- (age * 0.11) + (gender * 10.63) + ((weight/height^2) * 0.05) + 19.66
Right Elbow Extension	- (age * 0.08) + (gender * 8.33) + ((weight/height^2) * 0.16) + 12.37
Left Elbow Extension	- (age * 0.07) + (gender * 8.18) + ((weight/height^2) * 0.17) + 11.32
Right Hip Flexion	- (age * 0.33) + (gender * 19.19) + ((weight/height^2) * 0.66) + 34.44
Left Hip Flexion	- (age * 0.29) + (gender * 18.75) + ((weight/height^2) * 0.47) + 36.05
Right Hip Extension	-(age * 0.21 + (gender * 15.19) + ((weight/height^2) * 0.14) + 33.52
Left Hip Extension	-(age * 0.23) + (gender * 15.02) + ((weight/height^2) * 0.17) + 33.88
Right Knee Flexion	-(age * 0.16) + (gender * 8.78) + ((weight/height^2) * 0.08) + 22.47
Left Knee Flexion	-(age * 0.17) + (gender * 7.67) + ((weight/height^2) * 0.14) + 21.10
Right Knee Extension	- (age * 0.38) + (gender * 18.44) + ((weight/height^2) * 0.62) + 34.41
Left Knee Extension	- (age * 0.38) + (gender * 17.68) + ((weight/height^2) * 0.62) + 33.61

(NIMS 1996)
Strength prediction results in kilograms (kg)
Age = years; gender: male = 1, female = 0; weight = kg;; height = meters

Note: Age, height and weight values collected at the Baseline visit will be used for the calculation of predicted values for elbow flexion, elbow extension, hip flexion, hip extension, knee flexion and knee extension for all study time points.

Gross Grip

Normative grip strength values for the Jamar dynamometer for clinical use (in pounds)

	Females (n = 355)			Males (n = 365)		
Age (years)	**Number of subjects**	**5th %ile Jamar values (lbs)**	**Median Jamar values (lbs)**	**Number of subjects**	**5th %ile Jamar values (lbs)**	**Median Jamar values (lbs)**
20 - 29	51	50	62	50	81	100
30 – 39	50	49	64	51	80	105
40 – 49	50	48	63	50	78	107
50 – 59	51	45	61	54	73	104
60 – 69	49	40	56	58	64	95
70 - 79	50	32	46	50	51	77
≥ 80	54	22	34	52	34	54

(Peters et al. 2011)

Note: The age category that applies for a subject at the Baseline visit will be used for the calculation of predicted grip values for all study time points.

Walking Ability

Calculation of Predicted Six-Minute Walk Test Distance

6MWT Distance (meters) = 868.8 - (2.99*Age) – (74.7*Gender)

Age in years. Men = 0 and Women = 1.

Gibbons WJ, Fruchter N, Sloan S, Levy RD. Reference Values for a Multiple Repetition 6-Minute Walk Test in Healthy Adults Older than 20 Years. J Cardpulm Rehabil. 2001 Mar/Apr; 21(2):87-93

Note: The age of a subject at the Baseline visit will be used for the calculation of 6MWT predicted values for all study time points.

Table 6: Regression Equations and Multiple Correlations of Sex, Age, and Weight with Muscle Strength (Newtons)

Muscle Action	Side	Equation*	R	R^2
Wrist extension	Non	114.36 − 45.1S − .774A + .094W	.825	.680
	Dom	123.65 − 48.5S − .784A + .092W	.826	.683
Elbow flexion	Non	188.25 − 89.2S − .650A + .132W	.882	.779
	Dom	188.36 − 96.5S − .610A + .140W	.907	.822
Elbow extension	Non	150.37 − 71.5S − 1.044A + .126W	.852	.726
	Dom	156.49 − 73.0S − 1.032A + .116W	.853	.727
Shoulder lateral rotation	Non	140.32 − 50.2S − 50.164A + .080W	.786	.618
	Dom	147.66 − 54.5S − .930A + .088W	.810	.656
Shoulder extension	Non	260.18 − 113.5S − 1.868A + .202W	.842	.709
	Dom	278.99 − 120.0S − 1.99A + .202W	.855	.731
Shoulder abduction	Non	165.16 − 74.9S − .910A + .126W	.843	.710
	Dom	178.90 − 77.1S − 1.128A + .134W	.843	.710
Ankle dorsiflexion	Non	302.54 − 60.9S − 2.203A + .159W	.742	.550
	Dom	285.46 − 47.6S − 2.367A + .193W	.669	.448
Knee extension†	Non	480.70 − 95.0S − 4.868A + .310W	.826	.683
	Dom	465.22 − 84.7S − 4.803A + .325W	.820	.673
Hip flexion	Non	216.48 − 74.6S − .926A + .026W	.718	.516
	Dom	219.30 − 72.6S − .977A + .027W	.731	.534
Hip abdcution	Non	203.32 − 73.3S − 1.247A + .192W	.794	.630
	Dom	195.24 − 62.4S − 1.184A + .198W	.764	.584

*S, sex (male = 0, female = 1); A, age (years); W, weight (Newtons).
†The equations for knee extension are compromised by the upper limit of force (650N) recorded for 21 subjects.

Wrist extension (Bohannon 1997a)

Pinch Strength Norms for Adults

Average Performance of All Subjects on Key Pinch (kg.)

		Men			Women		
Age	Hand	Mean	SD	Range	Mean	SD	Range
20-24	R	11.8	1.6	9.5-15.4	8.0	0.9	6.4-10.4
	L	11.2	1.5	8.6-14.1	7.3	1.0	5.9-10.4
25-29	R	12.1	2.2	8.6-18.6	8.0	1.0	6.4-10.0
	L	11.3	2.0	8.6-17.7	7.5	1.0	5.9-10.0
30-34	R	12.0	2.2	9.1-16.3	8.5	1.4	5.9-11.3
	L	11.9	2.3	7.7-16.3	8.1	1.6	5.4-11.8
35-39	R	11.8	1.5	9.5-14.5	7.5	0.9	5.4-9.5
	L	11.6	1.8	8.2-14.5	7.3	1.2	5.4-10.0
40-44	R	11.6	1.2	9.5-14.1	7.6	1.4	4.5-10.9
	L	11.4	1.8	8.6-14.1	7.2	1.4	3.6-10.0
45-49	R	11.7	1.8	8.6-15.9	8.0	1.5	5.9-10.9
	L	11.2	2.0	8.2-19.1	7.5	1.3	5.4-10.9
50-54	R	12.1	2.0	9.1-15.4	7.6	1.1	5.4-10.0
	L	11.8	1.9	9.1-16.8	7.3	1.2	5.4-10.0
55-59	R	11.0	1.9	8.2-15.4	7.1	1.1	5.0-9.5
	L	10.4	2.1	5.9-14.1	6.7	1.0	5.4-8.6
60-64	R	10.5	2.4	6.4-16.8	7.0	1.2	4.5-9.1
	L	10.1	1.9	7.3-15.0	6.4	1.1	4.5-8.6
65-69	R	10.6	1.8	7.7-14.5	6.8	1.2	4.5-9.5
	L	10.0	1.6	7.7-12.7	6.5	1.3	4.5-9.1
70-74	R	8.8	1.1	7.3-11.3	6.6	1.3	3.6-10.0
	L	8.7	1.4	5.9-12.7	6.3	1.4	4.1-10.0
75 +	R	9.3	2.1	4.1-14.1	5.7	1.0	3.6-7.7
	L	8.7	1.4	5.9-10.9	5.2	1.2	3.2-7.3

The above information is taken from ***Grip & Pinch Strength: Normative Data for Adults***, Arch Phys Med Rehabil 66:69-72, 1985, V. Mathiowetz,et al

10.4 Summary of Efficacy Assessment in Parent Studies and in Current Study CL302

Study	Functional Test	Questionnaire	Biomarker
CL-202	Week 0, 12, 36, 60, 84, 108, 132, 156 Muscle strength as measured by HHD; Walking ability as measured by the 6MWT; Arm raising ability as measured by the weighted arm lift test; Functional disability as measured by the GNEM-FAS.	Week 0, 12, 36, 84, 156 None	Week 0, 12, 16, 36, 60, 108, 156 CK Free Serum SA Free and total urine SA (Part I only, Week 0, 12) Serum protein markers (Part I only, Week 0, 12)
CL-301	Week 8, 16, 24, 32, 40, 48 Muscle strength as measured by HHD; Walking ability as measured by the 6MWT; Arm raising ability as measured by the weighted arm lift test; Muscle strength on mobility domain score by GNEM-FAS	Week 8, 16, 24, 32, 40, 48 The total score on a 45-item self-report of INQoL. Week 24, 48 The CGI Severity scale (CGI-S, baseline only), and improvement scale (CGI-I, at each subsequent visit).	Week0, 8, 16, 24, 32, 40, 48 CK Serum SA Week0, 16, 32, 48 Free, total and bound urine SA Urine ManNAc
CL-203	Week 0, 12, 24, 36, 48 Muscle strength by GNEM-FAS Expanded Version total score; Upper extremity strength as measured by HHD Lower extremity muscle strength as measured by HHD	Week 0, 12, 24, 36, 48 Health-related quality of life as assessed by SF-36 Symptom severity as measured by PGI-S (baseline only) and PGI-C (at each subsequent visit)	Week 0, 12, 24, 36, 48 CK Free serum SA Serum aceneuramic acid Free, total and bound Urine SA Urine ManNAc
CL-302 (Patients from 202/301)	Week 0, 8, 16, 24, 48, 72, 96 Muscle strength as measured by HD; Walking ability as measured by the 6MWT; Arm raising ability as measured by the weighted arm lift test; Change in muscle strength on mobility domain score by GNEM-FAS.	Week 0, 8, 16, 24, 48, 72, 96 The total score on a 45-item self-report of INQoL.	Week 0, 8, 16, 24, 48, 72, 96 CK Free serum SA. Urine ManNAc

Study	Functional Test	Questionnaire	Biomarker
CL-302 (Patients from CL203)	Week 0, 24, 48, 72, 96 Muscle strength in GNEM-FAS Expanded Version total score; Muscle strength as measured by HHD.	Week 0, 24, 48, 72, 96 Health-related quality of life as assessed by SF-36	Week 0, 8, 16, 24, 48, 72, 96 CK Free serum SA. Urine ManNAc

10.5 Schedule of Events

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

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

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

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

a. Potential subjects can be screened up to 5 days after the last dose on the parent study. Baseline Visit should be not be more than 5 days after Screening visit. Subjects can have a concurrent Screening and Baseline visits. Study drug will be dispensed only after all study procedures at the Baseline Visit have been performed. For subjects who discontinue prior to completing the study, every reasonable effort should be made to perform the Early Termination (ET) procedures within four weeks of discontinuation.
b. Interval history will include any signs, symptoms, or events (i.e. falls) experienced by the subject since the prior study visit that are not related to study procedure(s) performed at prior study visits or study drug. Interval history may include exacerbation or improvement in existing medical conditions (including the clinical manifestations of GNEM) that might interfere with study participation, safety, and/or positively or negatively impact performance of functional assessments.
c. The physical examinations at Baseline/Screening, including a neurological examination; all others will be brief physical examinations. If a patient is unable to stand or has significant postural issues that interfere with collection of a standing height, self-reported adult height should be captured.
d. Baseline C-SSRS administered at Baseline/Screening visit (may be same as last visit in parent study). Since Last Visit C-SSRS administered at all subsequent visits.
e. Serum will be obtained at all study visits to evaluate creatine kinase (CK), serum SA and potential biomarkers of sialylation, and other markers of muscle injury and remodeling.
f. Blood samples, preferably pre dose, and first-morning void urine will be collected to assess trough SA levels; record volume of urine collected.
g. An aliquot from first morning void urine will be used for assessment of ManNAc; record volume of urine collected.
h. Subjects should be instructed to return unused study drug and packaging to every visit. Note that all subjects being treated with 12 g/day Ace-ER in UX001-CL202 will be transitioned to 6 g/day Ace-ER dose in this protocol.
i. For UX001-CL202 subjects, assessments that cannot be safely performed by a subject due to disease progression should not be administered.
j. For subjects enrolling from UX001-CL203, lower extremity muscle strength for knee extensors muscle group only.
k. For subjects enrolling from UX001-CL203, the GNEM-FAS Expanded version will be used.
l. The Early Termination Visit occurs if a subject discontinues prior to completing the study or no longer wants to participate in the study. Every reasonable effort should be made to have subjects return to the clinic within 4 weeks of discontinuation and perform the Early Termination procedures; however, subjects who are unable to return to the clinic will be given the option of having an Early Termination Visit telephone call within 4 weeks of discontinuation from study, where appropriate information will be collected by the clinical site.
m. Safety Follow-up visit to be conducted by phone 30 days (+5 days) after last dose of study drug.

10.6 Adverse Events to Monitor

10.6.1 Gastrointestinal MedDRA Query

The following MedDRA PTs are included in the gastrointestinal SMQ version 17.1.

Narrow Scope	Broad Scope
Abdominal discomfort	Anorectal swelling
Abdominal distension	Antacid therapy
Abdominal pain	Antidiarrhoeal supportive care
Abdominal pain lower	Antiemetic supportive care
Abdominal pain upper	Breath odour
Abdominal symptom	Chest pain
Abdominal tenderness	Colonic lavage
Abnormal faeces	Dysphagia
Aerophagia	Early satiety
Anorectal discomfort	Gastritis prophylaxis
Bowel movement irregularity	Gastrointestinal disorder therapy
Change of bowel habit	Gastrointestinal tract irritation
Constipation	Gastrooesophageal reflux prophylaxis
Defaecation urgency	Glycogenic acanthosis
Diarrhoea	Hypovolaemia
Epigastric discomfort	Laxative supportive care
Eructation	Malabsorption
Faecal volume decreased	Mucous stools
Faecal volume increased	Oesophageal polymer implantation
Faeces hard	Pernicious anaemia
Faeces soft	Post procedural constipation
Flatulence	Post procedural diarrhea
Frequent bowel movements	Post-tussive vomiting
Gastrointestinal pain	Probiotic therapy
Gastrointestinal sounds abnormal	Procedural nausea
Gastrointestinal toxicity	Procedural vomiting
Infrequent bowel movements	Prophylaxis against diarrhoea
Nausea	Prophylaxis of nausea and vomiting
Non-cardiac chest pain	Regurgitation
Oesophageal discomfort	Retching
Oesophageal pain	Steatorrhoea
Premenstrual cramps	Vomiting projectile
Vomiting	

10.6.2 Liver-Related Investigations

The following MedDRA PTs are included in the category "liver-related investigations."

Alanine aminotransferase abnormal
Alanine aminotransferase increased
Aspartate aminotransferase abnormal
Aspartate aminotransferase increased
Gamma-glutamyl transferase abnormal
Gamma-glutamyl transferase increased
Hepatic enzyme abnormal
Hepatic enzyme increased
Liver function test abnormal
Transaminases abnormal
Transaminases increased

10.7 Table templates for efficacy and safety analysis presentation

Table 14.x.x.x
Summary of HHD Upper Extremity Component (UEC) Scores – Parent Study CL301
(Full Analysis Set)

	ACE-ER 6 g/day				
	Treatment in Parent Study CL301 (Parent study baseline)		Treatment in Parent Study CL301 (Current study baseline)		
Visit Statistics	Placebo (N=xx)	Ace-ER 6 g/day (N=xx)	Placebo (N=xx)	Ace-ER 6 g/day (N=xx)	Total
Week 8					
n	xx	xx	xx	xx	xx
Mean	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
SD	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
Median	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Change from Baseline to Week 8					
……					
Week 96					

SD=standard deviation.
Study UX001-CL301 is a placebo-controlled efficacy study.

Table 14.x.x.x
Summary of HHD Upper Extremity Component (UEC) Scores – Parent Study CL202
(Full Analysis Set)

Visit Statistics	Ace-ER 6 g/day Current Study Baseline (N=xx)
Week 8	
n	xx
Mean	xx.xx
SD	xx.xxx
Median	xx.xx
Min, Max	xx.x, xx.x
Change from Baseline to Week 8	
……	
Week 96	

SD=standard deviation.
Study UX001-CL202 is an extension study of CL201 with 10 naïve subjects.

Table 14.x.x.x
Summary of HHD Individual Raw Strength Scores: Knee Extensors – Parent Study CL203
(Full Analysis Set)

Visit Statistics	Ace-ER 6 g/day Parent Study Baseline (N=xx)	 Current Study Baseline (N=xx)
Week 24		
n	xx	xx
Mean	xx.xx	xx.xx
SD	xx.xxx	xx.xxx
Median	xx.xx	xx.xx
Min, Max	xx.x, xx.x	xx.x, xx.x
Change from Baseline to Week 24		
……		
Week 96		

SD=standard deviation, Min=minimum, Max=maximum.
Study UX001-CL203 is a safety study.

Table 14.x.x.x
Overall Summary of Treatment Emergent Adverse Events
(Safety Analysis Set)

	Ace-ER 6 g/day					
	Treatment in Parent Study CL301			Parent Study		
	Placebo (N=xx) n (%)	Ace-ER 6 g/day (N=xx) n (%)	All (N=xx) n (%)	CL202 (N=xx) n (%)	CL203 (N=xx) n (%)	Total (N=xx) n (%)
Number of subjects with TEAEs	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Maximum severity						
Grade 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Grade 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Grade 3	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Grade 4	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Grade 5	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Number of subjects with treatment-related TEAEs	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Number of serious TEAEs	xx	xx	xx	xx	xx	xx
Number of subjects with serious TEAEs	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Number of TEAEs causing discontinuation	xx	xx	xx	xx	xx	xx
Number of subjects with TEAEs causing discontinuation	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)