16.1.9 Documentation of Statistical Methods

16.1.9.1 Statistical Analysis Plan

Statistical Analysis Plan, V 1.0, dated 15 March 2017

STATISTICAL ANALYSIS PLAN

Title	**A Phase 2 Open-label study to Evaluate Safety of Aceneuramic Acid Extended Release (Ace-ER) Tablets in GNE Myopathy (GNEM) (also known as Hereditary Inclusion Body Myopathy (HIBM)) patients with Severe Ambulatory Impairment**
Protocol:	**UX001-CL203**
Protocol Version	**Amendment 1 (15 March 2017)**
Investigational Product:	**Aceneuramic Acid Extended Release (Ace-ER)**
Phase:	**2**
Sponsor:	**Ultragenyx Pharmaceutical Inc.** **60 Leveroni Court** **Novato, CA, USA 94949**
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Date:	**29 March 2017**
Version Number:	**1.0**

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ABBREVIATIONS

6MWT	six minute walk test
Ace-ER	Aceneuramic Acid Extended Release
AE	adverse event
ANCOVA	analysis of covariance
ATC	Anatomic Therapeutic Classification
CK	creatine kinase
CMH	Cochran-Mantel-Haenszel
CRF	case report form
CSR	clinical study report
C-SSRS	the Columbia Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
DMC	data monitoring committee
ECG	electrocardiogram, electrocardiographic
GEE	generalized estimating equations
GNE	glucosamine (UDP-N-acetyl)-2-epimerase
GNEM	GNE myopathy
HIBM	hereditary inclusion body myopathy
INQoL	individual neuromuscular quality of life questionnaire
IWRW	interactive web randomization system
MedDRA	medical dictionary of regulatory activities
MMRM	mixed-effects model for repeated measures
QIC	Quasi-Likelihood Information Criterion
PD	pharmacodynamics
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	pharmacokinetic
PRO	patient reported outcomes
PT	preferred term
SA	sialic acid
SAE	serious adverse event

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SA-ER	sialic acid-extended release
SAP	statistical analysis plan
SI	*Le Système International d'Unités* (International System of Units)
SMQs	Standardized MedDRA Queries
SOC	system organ class
TEAE	treatment-emergent adverse even

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-CL203 original protocol dated 04 December 2015 and protocol Amendment 1 dated 15 March 2017.

The data collected in this study will be used to evaluate the safety of Aceneuramic Acid Extended Release (Ace-ER) Tablets in GNE Myopathy (GNEM) (also known as Hereditary Inclusion Body Myopathy (HIBM)) patients with Severe Ambulatory Impairment. 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. Should there be a difference between the SAP and the protocol with respect to analysis methods, the SAP will take precedence over the protocol.

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2 STUDY OBJECTIVE(S)

2.1 Primary Objective

Evaluate the safety of Ace-ER in GNEM subjects with severe ambulatory impairment.

2.2 Secondary Objective

Evaluate the potential efficacy of 6 g/day of Ace-ER in GNEM subjects with severe ambulatory impairment.

2.3 Exploratory Objectives

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

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3 STUDY DESIGN

UX001-CL203 is an open-label, multicenter study to assess the safety of Ace-ER in GNEM patients with severe ambulatory impairment. Efficacy will also be assessed as a secondary objective. Approximately 45 subjects will be enrolled in the study and receive 6 g/day of Ace-ER for 48 weeks.

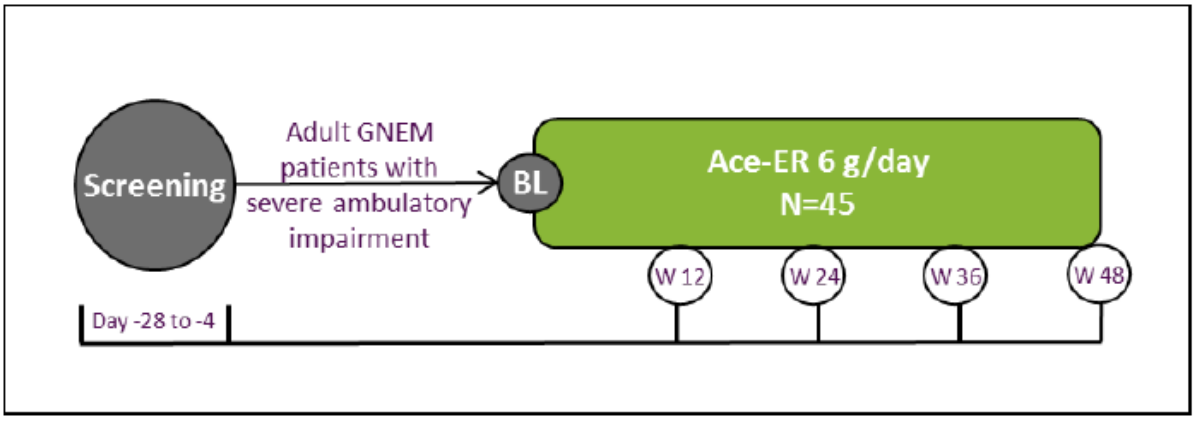
Subjects will take 4 tablets (500 mg each for 2 g per dose) orally 3 times per day (TID). The dose should be taken with food (i.e. within 30 minutes after a meal or snack). Treatment will be administered for a total of 48 weeks. Study visits will occur every 12 weeks during the Treatment Period during which the scheduled assessments will be administered as outlined in the Schedule of Events (Appendix 10.5).

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

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

Efficacy will be evaluated by dynamometry as a measure of muscle strength and patient-reported outcome measures as measures of physical functioning and quality of life. Figure 3.1 provides a schematic of the study design. The schedule of assessments is shown in Appendix 10.5.

Figure 3.1: Study Schema



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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) and meet the criteria for severe ambulatory impairment defined in protocol.

3.2 Dosage and Administration

The 6 g/day Ace-ER dose has been selected. Individual subject participation in this study will be a maximum of 56 weeks, including up to 4 weeks between Screening and Baseline, 48 weeks of treatment, and a Safety Follow-up Visit occurring 4 weeks after last study drug administration.

3.3 Blinding and Randomization Methods

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

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

3.5 Interim Analysis

No interim analysis is planned for this study.

4 STUDY ENDPOINTS AND COVARIATES

All data are collected according to the schedule of assessments (Appendix 10.5).

4.1 Primary Endpoints

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.

4.2 Secondary Endpoints

The secondary safety endpoints of the study are clinically significant changes from baseline to scheduled time points in:

- Concomitant medications;
- Physical examinations;
- Vital signs,
- Clinical laboratory results;
- Interval history.

The secondary efficacy endpoints of the study are changes from baseline over the duration of the study:

- Changes from baseline in the total scores and scores on the mobility, self-care and upper extremity domains 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.

4.3 Exploratory Endpoints

The exploratory endpoints of the study include health related QoL, patient reported outcomes and biomarkers as listed below:

- 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 symptom severity score as measured by Patient Global Impression of Severity (PGI-S) and Patient Global Impression of Change (PGI-C) over the duration of the study;
- Changes from baseline in serum biomarkers: creatine kinase (CK), serum SA, and potential biomarkers of sialylation and other markers of muscle injury and remodeling;

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- Changes in free serum SA levels to assess the drug concentration in the bloodstream resulting from treatment;
- Frequency and percentage of subjects with the presence of ManNac detected from urine testing.

4.4 Covariate(s)

All models used for each individual clinical endpoint will incorporate the baseline value as a covariate.

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5 DEFINITIONS

5.1 Baseline

Baseline is defined as the last non-missing measurement taken prior to the first dose of study drug administration in CL203 study

5.2 UX001 Treatment Start/END Date

The treatment start date is defined as the first dosing date of study drug recorded in the EDC database. The treatment end date is defined as the last dosing date of study drug recorded in the EDC database. For each subject, the total duration of study drug exposure is defined as the sum of exposures.

5.3 Derived Efficacy Variables

5.3.1 Predicted Normal HHD values

- **HHD Individual Muscle Strength Average Score** is calculated as the average of the right and left raw measurements in kg for an individual muscle group: individual muscle strength raw score = (left-side measurement + right-side measurement) / 2. If a value from the right or left side of an individual muscle group is missing, the missing value will be imputed using the non-missing value from the other side.
- **Predicted Normal HHD Values** will be derived for the raw right/left strength values from the muscle groups: grip, key pinch, shoulder abductors, wrist extensors and knee extensors collected at Baseline using the regression equations outlined in Appendix 10.2. Predicted normal HHD scores for individual muscle raw score will use the same computation method for raw scores as described above but replace the observed values with the predicted normal HHD values.
- **% of Predicted Normal HHD Values** for the individual muscle groups and composite scores will be calculated as follows: (Observed Value / Predicted Normal HHD Value) *100%. Baseline predicted normal values will be used to derive % of predicted normal values for all post-baseline study time points.

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6 ANALYSIS POPULATIONS

6.1 Full Analysis Set

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

6.2 Safety Analysis Set

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

6.3 Sialic Acid Analysis Set

The SA analysis set will consist of all enrolled subjects with evaluable free serum SA levels.

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7 DATA SCREENING AND ACCEPTANCE

7.1 General Principles

Data will be reviewed periodically. Any questionable data will be reported to clinical data manager promptly.

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 a review of tables and listings for this study. Missing and incomplete data will be identified for investigation, and possible resolution, by Data Management prior to the study database lock.

Missing or invalid safety events and assessments will not be imputed or replaced. Missing measurements in HHD individual muscle group test will be imputed as 0 if the reason for missing is due to weakness. When the measurement for one side is missing, the measurement from the other side will be used to impute the missing value. Details of missing observation handling in HHD are provided in Appendix 10.3. Other efficacy endpoints will not be imputed.

7.2.1 Missing Date of the Last Dose of Investigational Product

When the date of the last dose of investigational product is 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 Medical History Related Dates (eg, diagnosis date) or Birth Date

- If only the day is missing, impute the day to first day of the month.
- If day and month are missing, impute to the 1st January.
- If year is missing, then no imputation will be done, the date will be missing.

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

7.2.3 Missing Date 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.

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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 double-blind 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 scheduled 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 Testing/Validation Plan

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

7.4 Software

SAS® software version 9.4 or higher will be used to perform all statistical analyses.

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8 STATISTICAL METHODS OF ANALYSES

8.1 General Principles

The statistical analyses will be reported using summary tables, figures, and data listings. Statistical tests, if any, will be 2-sided at the 5% level of significance. All p-values will be presented as nominal p-values. No adjustment on multiplicity will be made. Confidence intervals will be 2-sided 95% confidence intervals, unless stated otherwise. 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.

The final analysis will be conducted when all patients enrolled in the study have completed the Week 48 visit or have discontinued the study.

8.2 Repeated Measure Model: General Estimating Equations

The efficacy endpoints are collected over time and will be analyzed using a generalized estimation equation (GEE) model that includes time as the categorical variable and adjusted for baseline measurement. The covariance structure that will be used for the GEE model is compound symmetry which specifies constant variance for the assessments and constant covariance between the assessments over time. If the compound symmetry covariance structure leads to non-convergence, Quasi-Likelihood Information Criterion (QIC) will be used to select the best covariance structure. Model based estimates of the changes from baseline and corresponding 95% confidence intervals will also be provided along with p-values for assessing statistical significance.

8.3 Subject Disposition

Subject disposition summaries will include the number of subjects who received study medication, the number of subjects who completed the study, and the reasons for study discontinuation. The number of subjects included in the safety, efficacy, and SA analyses, respectively, will be presented.

8.4 Protocol Deviations

Protocol deviations will be listed.

8.5 Demographic and Baseline Characteristics

The following key demographic and baseline factors will be summarized descriptively for the Full Analysis Set:

- Gender
- Age

- Ethnicity/Race
- Age at diagnosis
- Age at start of treatment
- Height (cm)
- Weight (kg)

8.6 Disease Characteristics and Medical History

Disease characteristics and medical history of GNEM including GNEM symptoms, adaptations, assisted devices, orthotics, medications, and treatment history will be summarized for the Full Analysis Set.

8.7 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.

Dosing compliance will also be summarized for the Safety Analysis Set. The compliance for each subject is defined as:

Compliance = Total Dose Received / Total Dose Planned * 100%.

8.8 Efficacy Analyses

For each efficacy endpoint, summary statistics will be reported at each visit for the observed measures and their respective changes from baseline.

The efficacy endpoints measured over time will be analyzed using GEE using the Full Analysis Set. Changes from baseline will be the dependent variable, and baseline, visit will be the independent variables in the model. All efficacy endpoints were assessed at Baseline, Week 12, Week 24, Week 36, and Week 48.

8.8.1 Dynamometry

Hand held dynamometry testing of multiple muscle groups will be used to measure strength. Test administration at the Screening visit is intended to provide experience and familiarize the subject with the assessments for the evaluator and the subject and data collected will not be used for analysis. The maximum voluntary isometric contraction (MVIC) against a dynamometer will be used to measure bilateral strength in the following muscle groups: shoulder abductors, wrist extensors and knee extensors. Specialized dynamometers for the measurement of grip and key pinch strength will also be used. The total force (in kg) for each 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

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after the testing using published normative data (Appendix 10.2). Missing measurements in dynamometry will be handled according to specified rules in the Appendix 10.3.

8.8.2 GNEM-FAS Expanded Version

The original GNEM-FAS was developed as a clinician-reported outcome measure (ClinRo) for ambulatory GNEM patients but has since been modified to include additional items to accommodate weaker patients. This modified version is referred to as the GNEM-FAS Expanded Version and will be used in this study. The scale consists of 3 domains: upper extremity, mobility, and self-care; scores for each domain and a total score will be calculated. Test administration at Screening Visit is intended as practice for the evaluator and the subject, and data collected will not be used for analysis. The GNEM-FAS Expanded Version used in this study is a modified version of the original GNEM-FAS with added questions to accommodate weaker patients. Three items regarding sitting ability were added to mobility domain; one item of picking up small items was added to upper extremity domain; and one item of chewing and swallowing was added to self-care domain.

8.9 Exploratory Analyses

The exploratory endpoints of the study include health related QoLs (SF-36v2, PGI-S and PGI-C) and biomarkers. The exploratory efficacy analyses will be mostly performed in descriptive statistics. Analysis for SF-36v2can be performed in a similar fashion as described for secondary efficacy analyses if appropriate.

8.9.1 Short Form - 36 Health Survey

The Short Form -36 Health Survey (SF-36v2) version 2 is a validated 36-item questionnaire that yields an 8-domain scale scores and two component summary measures of health-related quality of life. It will be evaluated at Baseline, Week 12, Week 24, Week 36, and Week 48. The domain scales are as follows:

- Physical Functioning (PF): Items 3a, 3b, 3c, 3d, 3e, 3f, 3g, 3h, 3i, 3j .
- Role-Physical (RP): Items 4a, 4b, 4c, 4d.
- Bodily Pain (BP): Items 7, 8.
- General Health (GH): Items 1, 11a, 11b, 11c, 11d.
- Vitality (VT): Items 9a, 9e, 9g, 9i.
- Social Functioning (SF): Items 6, 10.
- Role-Emotional (RE): Items 5a, 5b, 5c.
- Mental Health (MH): Items 9b, 9c, 9d, 9f, 9h

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The overall summary measures are as follows:

- Physical Health Component Score (PCS): domain scales PF, RP, BP, GH.
- Mental Health Component Score (MCS): domain scales VT, SF, RE, MH.

Descriptive summary statistics and GEE modeling will be presented for the eight scale scores and PCS and MCS component scores at each time point as well as the change from baseline.

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

The PGI-S/PGI-C is a self-administered tool widely used in chronic pain clinical trials to indicate the patient's perception about the efficacy of treatment. The PGI-S is conducted at baseline and patient rates the severity of his/her condition on a 7-point categorical scale; the PGI-C is conducted at follow-up visits and a patient rate the change of his/her condition on a 7-point categorical scale. The scales are presented in the table below.

Summary statistics of baseline PGI-S will be reported. The number and percentage of subjects in each category of PGI-S will also be reported. For PGI-C, both summary statistics and GEE estimates will be presented for each time point.

PGI-S	PGI-C
1=Normal, not affected at all	-3=Very much worse
2=Borderline affected	-2=Much worse
3=Mildly affected	-1=Somewhat worse
4= Moderately affected	0=No change
5=Markedly affected	+1=Somewhat better
6=Severely affected	+2=Much better
7=Extremely affected	+3=Very much better

8.9.3 Biomarkers and Drug Concentration Measurements

Serum Creatine Kinase (CK), serum SA, and urine ManNAc will be collected at baseline, week 12, week 24, week 36, and week 48 or termination visit.

- Free SA: Free SA levels in serum assess the drug concentration in the bloodstream resulting from treatment and are the best indicator of compliance with the treatment regimen. Free SA levels in serum are expressed in micrograms of SA per ml of serum
- 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.
- Presence of ManNAc: To detect noncompliance with prohibited medication restrictions during the study period.

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The changes from baseline will be summarized and analyzed for the duration of the treatment using GEE.

8.10 Safety Analyses

Adverse event (AE) serves the primary endpoint of the study. Secondary endpoint of Safety Analysis summarizes clinically significant changes from baseline to scheduled time points in:

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

Safety endpoints will be analyzed by using descriptive statistics in the Safety Analysis Set.

8.10.1 Adverse Events

The following AEs will be collected:

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

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 number and proportion of subjects with any treatment-emergent adverse events (TEAEs) (defined as any AE occurred 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.

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.

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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.

8.10.1.1 Adverse Events to Monitor

Adverse events to be monitored are included in Appendix 10.7 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.

8.10.2 Laboratory Parameters

Clinical laboratory data will be summarized descriptively by the type of laboratory test and by time point. 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 reported by shift tables. 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.

8.10.3 Prior and Concomitant Medications

Prior medication is defined as any medication started before the date of the first dose of investigational product. Concomitant medication is defined as any medication taken on or after the date of the first dose of investigational product. Any concomitant medications started after the date of the last dose of investigational product will not be presented in the summary tables but will be included in the subject data listings.

Each medication will be coded to a preferred name and an Anatomic Therapeutic Classification (ATC) code using WHODrug. The number and percentage of subjects taking each concomitant medication will be displayed by preferred name. 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. Prior and concomitant medications will be listed.

8.10.4 Physical Examinations

Physical examinations will be performed at baseline, week 12, week 24, week 36, and week 48 or termination visit. At baseline and week 48, a full physical examination will be conducted including a neurological examination. A brief physical examination will be conducted at other visits. The full examination assesses the general appearance, HEENT, cardiovascular, dermatologic, lymphatic, respiratory, gastrointestinal, and musculoskeletal; the brief physical examination assesses the general appearance, cardiovascular, and respiratory; the neurological examination assesses the cognition, cranial nerves, motor

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function, coordination and gait, reflexes, and sensory function. Full physical and neurological examinations will be summarized using shift tables. Results from brief physical examinations will be listed.

8.10.5 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 and will be reported in a listing.

8.10.6 Interval History

Each interval history is intended to record 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 identify under-reported AEs. Interval history for all subjects will be reported in a listing.

8.10.7 Suicidal ideation and behavior

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) and will be administered at each visit. The C-SSRS will be listed.

8.10.8 Urine Testing for ManNAc

ManNAc will be assessed at each visit to detect noncompliance with prohibited medication restrictions. The ManNAc results for all subjects in the Safety Analysis Set will be reported in listing format.

8.10.9 Pregnancy Test

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

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9 REFERENCES

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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.

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.

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10 APPENDICES

10.1 Efficacy Endpoints Definition Details

10.1.1 GNEM Functional Activities Scale Expanded Version

The GNEM-FAS (also referred to as HIBM-FAS in some studies) expanded version is a disease-specific measure developed to assess the functional impact of changes in muscle strength. The scale consists of 3 domains: upper extremity, mobility, and self-care; scores for each domain and a total score will be obtained. The GNEM-FAS expanded version will be administered at each visit beginning with the Screening Visit to evaluate physical functioning. Test administration at the Screening visit is intended to provide experience and familiarize the subject with the assessments for the evaluator and the subject, and data collected will not be used for analysis. The scale has been developed specifically for patients with GNEM based on feedback received from affected individuals on the impact of the disease on their function. Items in the scale assess the subject's ability to independently perform various activities of living that involve self-care, mobility and use of the upper and lower extremities. The original GNEM-FAS was developed as a clinician-reported outcome measure (ClinRo) for ambulatory GNEM patients but has since been modified to include additional items to accommodate weaker patients. This modified version is referred to as the GNEM-FAS Expanded Version and will be used in this study.

GNEM Functional Activities Scale (GNEM-FAS) Expanded Version Total Score will be calculated as the sum of the Total Scores range from 0 to 120 with higher scores representing greater independence with functional activities. Subscale scores will be calculated for the Mobility, Upper Extremity and Self-Care domains. Mobility subscale scores have 13 items and range from 0 to 52 with higher scores representing greater mobility. Upper Extremity subscale scores have 9 items and range from 0 to 36 with higher scores representing more skilled, independent use of the arms during functional activity performance. Self-Care subscale scores have 8 items range from 0 to 32 with higher scores representing greater independence with functional care activities. The maximum possible for the total score is 120.

10.1.2 Short Form – 36 Item (SF-36)

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

The scale and component scores will be calculated according to the standard scoring algorithm published along with the SF-36 (Ware et.al. 1995 and Ware et.al. 2007). The z

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scores of domain scales will be aggregated to generate the component scores PCS and MCS using weights derived from the U.S. general population. The component scores will be scaled to have a mean of 50 and standard deviation of 10 using a linear transformation. The component scores will not be calculated unless all relevant domain scale scores are available. Details of the scoring algorithm can be found in Appendix 10.4.

10.2 Predicted HHD Normal Muscle Strength

Muscle strength of interest for this study includes grip, key pinch, shoulder abductors, wrist extensors, and knee extension.

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.

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

(Bohannon 1997)
*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 for all study time points.

Gross Grip

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

Age (years)	Females (n = 355)			Males (n = 365)		
	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.

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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 1997)

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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

10.3 Missing Observation in Hand Held Dynamometry

Missing observations in HHD 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 a joint 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 strength for this muscle group. The muscle group IS counted as part of the UE or LE composite.

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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 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 injury.

- 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 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 evaluator 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 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 strength for this muscle group. The muscle group IS counted as part of the UE or LE composite.

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10.4 SF-36 v2® Scoring Algorithm

Prior to any summary scores being calculated, ten items in the questionnaire will be re- coded according to the developer's instructions as follows:

	Response Choices	Pre-coded Item Value		Final Item Value
Item1	Excellent	1		5.0
	Very Good	2		4.4
	Good	3		3.4
	Fair	4		2.0
	Poor	5		1.0
Item 6	Not At All	1		5
	Slightly	2		4
	Moderately	3		3
	Quite A Bit	4		2
	Extremely	5		1
Item 7	None	1		6.0
	Very Mild	2		5.4
	Mild	3		4.2
	Moderate	4		3.1
	Severe	5		2.2
	Very Severe	6		1.0
Item 8	**If both item 7 and item 8 are answered**	**Item 8 pre-coded value**	**Item 7 pre-coded value**	
	Not At All	1	1	6
	Not At All	1	2 through 6	5
	A Little Bit	2	2 through 6	4
	Moderately	3	2 through 6	3
	Quite A Bit	4	2 through 6	2
	Extremely	5	2 through 6	1

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	Response Choices	Pre-coded Item Value	Final Item Value
Item 8	**If Item 7 is not answered**		
	Not At All	1	6.0
	A Little Bit	2	4.75
	Moderately	3	3.5
	Quite A Bit	4	2.25
	Extremely	5	1.0
Item 9a, 9d, 9e and 9h	All Of The Time	1	6
	Most Of The Time	2	5
	A Good Bit Of The Time	3	4
	Some Of The Time	4	3
	A Little Of The Time	5	2
	None Of The Time	6	1
Item 11b and 11d	Definitely True	1	5
	Mostly True	2	4
	Don't Know	3	3
	Mostly False	4	2
	Definitely False	5	1

Upon appropriate re-coding of individual items, the raw scale score will be calculated as the average score over non-missing items in that scale and scaled between 0 and 100, with higher score representing better health status. The raw scale score will not be calculated unless ≥ 50% of relevant questions are answered in a scale domain.

The raw scale scores will be computed by taking the sum of the items for that particular scale. Each raw scale score will then be transformed to a 0 to 100 scale using the following formula:

$$\text{Transformed Scale} = \frac{[\text{Actual raw score} - \text{Lowest possible raw score}]}{\text{Possible raw score range}} \times 100$$

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This information is summarized in the following table.

Formulae for Scoring and Transforming Scales			
Scale	**Sum Final Item Values**	**Lowest And Highest Possible Raw Scores**	**Possible Raw Score Range**
Physical Functioning (PF)	3a + 3b + 3c + 3d + 3e + 3f + 3g + 3h + 3I + 3j	10, 30	20
Role-Physical (RP)	4a + 4b + 4c + 4d	4, 8	4
Bodily Pain (BP)	7 + 8	2, 12	10
General Health (GH)	1 + 11a + 11b + 11c + 11d	5, 25	20
Vitality (VT)	9a + 9e + 9g + 9i	4, 24	20
Social Functioning (SF)	6 + 10	2, 10	8
Role-Emotional (RE)	5a + 5b + 5c	3, 6	3
Mental Health (MH)	9b + 9c + 9d + 9f +9h	5, 30	25

A norm-based z score for each scale will then be computed using the U.S. general population data for each scale score.

PF_Z = (PF - 84.52404) / 22.89490
RP_Z = (RP - 81.19907) / 33.79729
BP_Z = (BP - 75.49196) / 23.55879
GH_Z = (GH - 72.21316) / 20.16964
VT_Z = (VT - 61.05453) / 20.86942
SF_Z = (SF - 83.59753) / 22.37642
RE_Z = (RE - 81.29467) / 33.02717
MH_Z = (MH - 74.84212) / 18.01189

The z-scores for the raw scales will be combined to form the two raw summary scores by multiplying each one by its corresponding scoring coefficient from the general U.S. population and taking the sum of those values.

AGG_PHYS = (PF_Z * .42402) + (RP_Z * .35119) + (BP_Z * .31754) + (GH_Z * .24954) + (VT_Z * .02877) + (SF_Z * -.00753) + (RE_Z * -.19206) + (MH_Z * -.22069)

AGG_MENT = (PF_Z * -.22999) + (RP_Z * -.12329) + (BP_Z * -.09731) + (GH_Z * -.01571) + (VT_Z * .23534) + (SF_Z * .26876) + (RE_Z * .43407) + (MH_Z * .48581)

The general U.S. population means, standard deviations, and scoring coefficients are summarized in the following table:

			Factor Score Coefficients	
SF-36 Scale	Mean	SD	PCS	MCS
PF	84.52404	22.89490	0.42402	-0.22999
RP	81.19907	33.79729	0.35119	-0.12329
BP	75.49196	23.55879	0.31754	-0.09731
GH	72.21316	20.16964	0.24954	-0.01571
VT	61.05453	20.86942	0.02877	0.23534
SF	83.59753	22.37642	-0.00753	0.26876
RE	81.29467	33.02717	-0.19206	0.43407
MH	74.84212	18.01189	-0.22069	0.48581

Finally, the PCS and MCS will be standardized as follows:

PCS = (AGG_PHYS x 10) +50

MCS = (AGG_MENT x 10) +50

10.5 Schedule of Events

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

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

[a] Study assessments for a subject should be performed in a consistent order at each visit. Refer to the Clinical Evaluator Manual for additional details on specific assessments and the suggested order of administration.
[b] Potential subjects can be screened up to 28 days before the Baseline Visit.
[c] Baseline Visit should be at least 4 days after and within 28 days of Screening visit. Study drug will be dispensed only after all eligibility requirements are confirmed and study procedures at the Baseline Visit have been performed.
[d] The Early Termination Visit occurs if a subject discontinues prior to completing the study or no longer wants to participate in the study. Every reasonable effort should be made to have subjects return to the clinic within 4 weeks of discontinuation and perform the Early Termination procedures; however, subjects who are unable to return to the clinic will be given the option of having an Early Termination Visit telephone call (TC) within 4 weeks of discontinuation from study, where appropriate information will be collected by the clinical site.
[e] GNEM-specific medical history will include a detailed review of diagnostic and family history, as well as presenting symptoms and progression over time, and the use of assistive devices, drugs and therapies to manage the disease.
[f] If a patient is unable to stand or has significant postural issues that interfere with collection of a standing height, self-reported adult height should be captured
[g] Interval history will include any signs, symptoms, or events experienced by the subject since the prior study visit. Interval history may include exacerbation or improvement in existing medical conditions (including the clinical manifestations of GNEM) that might interfere with study participation, safety, and/or positively or negatively impact performance of functional assessments.

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

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

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

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

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

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

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

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

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

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

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

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10.6 Summary of Efficacy Endpoints and Analyses

Test / Instrument	Endpoint	Type of analysis	Time points for Assessment	Statistical approach at week 48/ET analysis
GNEM Functional Activities Scale (GNEM-FAS) – Expanded Version	Change from baseline in GNEM-FAS Expanded Version total score and mobility, upper extremity and self-care domain scores from baseline over the duration of the study	Secondary efficacy analysis	Baseline, Weeks 12, 24, 36, and 48	GEE Model / Descriptive statistics
Physical therapy – Hand-held Dynamometry (HHD)	Change from baseline in upper extremity strength in the following muscle groups: grip, key pinch, shoulder abductors and wrist extensors over the duration of study	Secondary efficacy analysis	Baseline, Weeks 12, 24, 36, and 48	GEE Model / Descriptive statistics
	Change from baseline in lower extremity muscle strength in the knee extensors as measured by HHD over the duration of the study			
	% of Predicted Normal HHD Values			
Medical Outcome Survey – 36 Items (SF-36)	Change in health-related quality of life as assessed by using SF-36 over the duration of the study	Exploratory efficacy analysis	Baseline, Weeks 12, 24, 36, and 48	GEE Model / Descriptive statistics
Patient Global Impression of Severity & Change (PGI-S & PGI-C)	Change in symptom severity as measured by PGI-S (baseline only) and PGI-C over the duration of the study	Exploratory efficacy analysis	Baseline, Weeks 12, 24, 36, and 48	Descriptive statistics

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10.7 Adverse Events to Monitor

10.7.1 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	

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10.7.2 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

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