STATISTICAL ANALYSIS PLAN

Protocol Title:	An Open-label Phase 2 Extension Study to Evaluate the Long Term Safety and Efficacy of Sialic Acid-Extended Release (SA-ER) Tablets and Sialic Acid-Immediate Release (SA-IR) Capsules in Patients with GNE Myopathy or Hereditary Inclusion Body Myopathy
Protocol Number:	UX001-CL202
Phase:	Phase 2 (Extension Study from UX001-CL201)
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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation/Term	Definition
6MWT	Six Minute Walk Test
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATS	American Thoracic Society
AUC	area under the curve
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CK	creatine kinase
CMP-SA	cytosine monophosphate-sialic acid
CRF	Case Report Form
CT	computed tomography
DMC	Data Monitoring Committee
DMRV	distal myopathy with rimmed vacuoles
EC	Ethics Committee
ELISA	enzyme-linked immunosorbent assay
EMG	electromyography
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GNE	glucosamine (UDP-N-acetyl)-2-epimerase
GNE-DMP	GNE Myopathy Disease Monitoring Program
GNE/MNK	glucosamine (UDP-N-acetyl)-2-epimerase/N-acetylmannosamine kinase
hERG	human ether-à-go-go-related gene
HHD	hand-held dynamometry
HIBM	hereditary inclusion body myopathy
HIBM-FAS	HIBM Functional Activities Scale
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure

Abbreviation/Term	Definition
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IND	Investigational New Drug (application)
IRB	Institutional Review Board
ITT	Intent-To-Treat Population
IVIG	intravenous immune globulin
LDH	lactate dehydrogenase
ManNAc	N-acetyl-D-mannosamine
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MMP9	matrix metallopeptidase 9
MRC	Medical Research Council
MUAP	polyphasic muscle unit action potential
MVIC	maximum voluntary isometric contraction
NANA	N-acetylneuraminic acid
NCAM	neural cell adhesion molecule
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOAEL	no observed adverse effect level
PD	pharmacodynamic
PK	pharmacokinetic(s)
PT	Preferred Term
qHS	at the time of sleep (i.e., at bedtime)
QID	four times per day
QD	one time per day
RBC	red blood cell
SA	sialic acid
SAE	serious adverse event
SA-ER	Sialic Acid-Extended Release
SA-IR	Sialic Acid Immediate Release
SAP	Statistical Analysis Plan

Abbreviation/Term	Definition
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SOC	System Organ Class
TID	three times per day
TNP	Treatment Niave Popultion
US	United States
WBC	white blood cell

1 INTRODUCTION

This document presents a statistical analysis plan (SAP) for Ultragenyx Pharmaceutical, Inc. Protocol UX001-CL202 (*An Open-label Phase 2 Extension Study to Evaluate the Long Term Safety and Efficacy of Sialic Acid-Extended Release (SA-ER) Tablets and Sialic Acid-Immediate Release (SA-IR) Capsules in Patients with GNE Myopathy or Hereditary Inclusion Body Myopathy*.

Reference materials for this statistical plan include the Protocol UX001-CL202 (Original: 01 March 2013, Amendment #1: 02 October 2013), UX001-CL202 Case Report Forms (24 July 2013), feeder study Protocol UX001-CL201 and the SAP for UX001-CL201 (05 November 2013: Week 48 Analysis). Study UX001-CL202 is an Open-Label extension study and treatment is not blinded. Subjects completing 48-week in study UX001-CL201 are eligible to continue treatment under this open-label extension protocol testing an increased dose of SA. Additional GNE Myopathy subjects will be enrolled to assess the safety and efficacy of SA-ER/SA-IR in a treatment naïve population. Ultragenyx Pharmaceutical is conducting UX001-CL202 in two parts:

- Part I of the study will provide additional information on the long-term safety and efficacy of 6g/day SA ER;

- Part II of the study will assess the safety and efficacy of 1.5 g of SA-ER / 1.5 g of SA-IR treatment 4 times per day (12g/day SA-ER/SA-IR total dose) for 6 months. If reasonable efficacy and safety are demonstrated at the interim analysis at 6 months post initiation of part II, the subjects may continue therapy for up to 36 months.

The statistical plan described hereafter is an *a priori* plan. The SAP will be finalized and approved prior to completing inferential or descriptive analyses of data pertaining Ultragenyx Pharmaceutical, Inc. Protocol UX001-CL202. Statistical Analysis programming may occur as study data accumulate in order to have analysis programs ready at the time the study finishes. For the reasons stated herein the conduct of the study in the field is considered to be independent of any study outcome that might materialize upon enactment of the currently proposed statistical analysis plan.

2 STUDY OBJECTIVES

Study objectives defined in the protocol and amendment include safety, clinical endpoints, and exploratory objectives for both Part I and Part II of the study. Objectives are specified as follows from the protocol:

1.1. Safety Objectives

- Evaluate additional long-term safety of SA-ER treatment of GNE Myopathy subjects previously treated with SA-ER at dose of 6g/day (Part I).

- Evaluate the safety of 12g /day SA-ER/SA-IR (delivered by 1.5g of SA-ER tablets and 1.5g of SA IR capsules 4 times per day) in the treatment of GNE Myopathy subjects over a 6 month treatment period (Part II).

1.2. Clinical Objectives

- Evaluate the long-term effect of SA-ER/SA-IR treatment of GNE Myopathy subjects on muscle strength as measured by hand-held dynamometry (HHD).

- Evaluate the long-term effect of SA-ER/SA-IR treatment of GNE Myopathy subjects on mobility, strength, and function using a series of physical performance measures.

- Evaluate the effect of SA-ER/SA-IR treatment of GNE Myopathy subjects on functional disability using an interview-based questionnaire.

1.3. Exploratory Objectives

- Evaluate the effect of SA-ER treatment on serum biomarkers of sialylation in GNE Myopathy subjects (Part I).

- Determine whether 12g/day SA-ER/SA-IR administered 1.5g/1.5g four times per day is superior to prior treatment with SA-ER in GNE Myopathy subjects (Part II).

3 STUDY DESIGN

As background for the statistical methods presented below, this section provides an overview of the study design and plan of study execution. The protocol (plus protocol amendment) is the definitive reference for all matters discussed in what follows.

UX001-CL202 open-label extension study will assess the long term safety and efficacy of SA ER/SA-IR treatment over a period of approximately 36 months, or until marketing approval or program termination by Ultragenyx. In Part I of the study, approximately 46 subjects will be enrolled following successful completion of the UX001-CL201 study. The Baseline visit will be conducted in conjunction with the UX001-CL201 Week 48 study visit to avoid treatment disruption. Enrollment will take place after all UX001-CL201 Week 48 study assessments have been completed and the investigator has determined the subject meets all eligibility criteria. Data collected at the UX001-CL201 Week 48 visit will serve as the Baseline data for Part I of this protocol. Following the signing of informed consent at the Baseline visit, each subject will be dispensed a 6-week supply of study drug. Throughout the Part I Treatment Period of the study, all subjects will continue to take four 500 mg SA-ER tablets orally three times per day (TID), in the morning, early evening, and at bedtime (qHS), for a total dose of 6g/day. The Part I Termination Visit will also serve as the Baseline Visit for Part II of the study. However, for completion of the analysis with integrated information from UX001-CL201 subjects the baseline may be defined as the week 48 visit from UX001-CL201, or other such baselines from key time points in the UX001-CL201 study as may be defined for selected analyses to examine clinical endpoints.

Beginning with the Part II-Baseline Visit, all subjects currently enrolled in Part I will crossover to the SA-ER/SA-IR dosing regimen. An additional 10 treatment naive GNE Myopathy subjects will be enrolled into Part II of the study. The additional subjects will provide an assessment of SA-ER/SA-IR treatment in SA naïve subjects able to walk at least 200 meters (and < 80% predicted) in a screening 6 Minute Walk Test (6MWT). Throughout the 36-month Part II Treatment Period, all subjects will be administered 1.5g SA-ER and 1.5g SA-IR orally four times per day (QID), in the morning, afternoon, early evening, and qHS, for a total SA dose of 12g/day.

Evaluations of safety, changes in clinical endpoints such as muscle strength, mobility, and function, and changes in exploratory serum biomarkers will be performed according to the Schedule of Events specific to each phase of the study. A Part II Termination Visit will be conducted 4 weeks after subjects receive their last dose of study drug. Efficacy data analyses will be conducted at the end of the 36-month Part II Treatment Period, although additional analyses may be performed and documented at the discretion of Ultragenyx.

Safety will be monitored throughout the study based on physical examinations, clinical laboratory analyses, and reporting of adverse events (AEs) and SAEs. An independent Data Monitoring Committee (DMC) will review safety information periodically an on an ad hoc basis as outlined in the DMC charter, which is maintained separately from this protocol.

A complete schedule of events specific for each part of the study is found in the protocol (Section 2, Tables 2.1 and 2.2) and repeated herein as Table 1 and Table 2.

Subjects enrolled in UX001-CL201 will roll over into UX001-CL202. In addition SA naïve treated subjects will be enrolled into Part II of UX001-CL202. Figure 1 presents a summary of the time points and dosing expected for subjects participating in UX001-CL0202, as well as outlining the key analysis time points: Additional analysis at 6 months after initiating Part II and the final analysis. (Note that the protocol refers to the 6 months analysis in Part II as an interim analysis. This analysis is being referred to as an additional analysis since this is an open label single arm study, and no formal adjustments for alpha spending will be employed in the study analyses).

Table 1 Schedule of Events (Part I)

ASSESSMENTS AND EVENTS	PART I TREATMENT PERIOD [b] (weeks)			PART I TERM VISIT [c]
	BASELINE [a]	6	12	
INFORMED CONSENT	X			
INTERVAL HISTORY [d]	X			X
VITAL SIGNS	X			X
HEIGHT AND WEIGHT	X			X
PHYSICAL EXAM [e]	X			X
NEUROLOGICAL EXAM	X			X
EFFICACY MEASURES				
HAND-HELD DYNAMOMETRY (HHD) [f]	X			X
6 MINUTE WALK TEST (6MWT) [f]	X			X
WALKING SPEED TEST [f]	X			X
WEIGHTED ARM LIFT TEST [f]	X			X
HIBM-FAS	X			X
CLINICAL LABORATORY TESTS				
CREATINE KINASE	X			X
SERUM PROTEIN MARKERS	X			X
FREE SERUM SA LEVELS [g]	X			X
FREE AND TOTAL URINE SA LEVELS [g]	X			X
CBC, CHEMISTRY, URINALYSIS	X			X
PREGNANCY TEST	X			X
ADVERSE EVENTS	X[h]	X	X	X
CONCOMITANT MEDICATIONS	X	X	X	X
TREATMENT DISPENSED	X	X	X	

[a] Potential subjects for the Part I Treatment Period will be baselined at the UX001-CL201 Week 48 study visit. Study drug will be dispensed only after UX001-CL202 consent has been signed and all study procedures have been performed.

[b] For Week 6 and 12 visits, the window is ± 0 days.

[c] The Part I Termination Visit will also serve as the Part II Baseline Visit. For subjects who discontinue prior to completing the study, the Termination Visit will be considered an Early Termination Visit; every reasonable effort should be made to perform the Termination Visit procedures within four weeks of discontinuation.

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

[e] The physical examinations at all study visits will be complete.

[f] Portions of the HHD, 6MWT, walking speed and weighted arm lift testing sessions may be videotaped to monitor administration technique and assess qualitative changes in function. Subject identity will be protected by blurring out the facial area in the video.

[g] Trough levels of free SA in serum and free and total SA in urine.

[h] Adverse Events will be collected after subject signs Informed Consent form.

Table 2 Schedule of Events (Part II)

Assessments and Events	Part II Treatment Period [b] (months)														Term Visit [c]
	Screening/ Baseline [a]	1	3	6	9	12	15	18	21	24	27	30	33	36	
Informed consent	X														
Medical/Interval History [d]	X	X		X		X		X		X		X		X	X
Vital signs	X	X		X		X		X		X		X		X	X
Height and Weight	X		X	X		X		X		X		X		X	X
Physical exam [e]	X			X				X						X	X
Neurological Exam	X			X				X						X	
Efficacy Measures															
Hand-Held Dynamometry (HHD) [f]	X		X	X		X		X		X		X		X	X
6 minute walk test (6MWT) [f]	X		X	X		X		X		X		X		X	X
walking speed test [f]	X		X	X		X		X		X		X		X	X
Weighted Arm Lift test [f]	X		X	X		X		X		X		X		X	X
HIBM-FAS	X			X				X						X	X
Clinical Laboratory Tests															
Creatine Kinase	X	X	X	X		X				X				X	X
Free Serum SA levels [g]	X	X	X	X		X				X				X	X
CBC, Chemistry	X	X	X	X		X				X				X	X
Pregnancy Test	X					X				X					X
Adverse Events	X [h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense Study Drug [i]	X	X	X	X	X	X	X	X	X	X	X	X	X		
Treatment Compliance [j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

[a] The Part I Termination Visit will also serve as the Part II Baseline Visit for continuing subjects. SA naïve subjects will enter directly into Part II of the study (Part II Screening/Baseline Visit). SA-ER/SA-IR study drug will be dispensed only after UX001-CL202 (Part II) consent has been signed and all study procedures have been performed.

[b] The Month 1 Visit window is ± 1 week. For all other Visits the window is ± 14 days.

[c] The Part II Termination Visit occurs four weeks after subjects receive their last dose. For subjects who discontinue prior to completing the study, the Termination Visit will be considered an Early Termination Visit; every reasonable effort should be made to perform the Termination Visit procedures within four weeks of discontinuation.

[d] For SA naïve subjects, medical history (including a detailed GNE Myopathy disease-specific history) will be reviewed at the Screening/Baseline visit. Interval history for all subjects will include any signs, symptoms, or events (e.g., falls) experienced by the subject since the prior study visit that are not related to study procedure(s) performed at prior study visits or study drug. Interval history may include exacerbation or improvement in existing medical conditions (including the clinical manifestations of GNE Myopathy) that might interfere with study participation, safety, and/or positively or negatively impact performance of functional assessments.

[e] The physical examinations at all study visits will be complete.

[f] Portions of the HHD, 6MWT, walking speed and weighted arm lift testing sessions may be videotaped to monitor administration technique and assess qualitative changes in function. Subject identity will be protected by blurring out the facial area in the video.

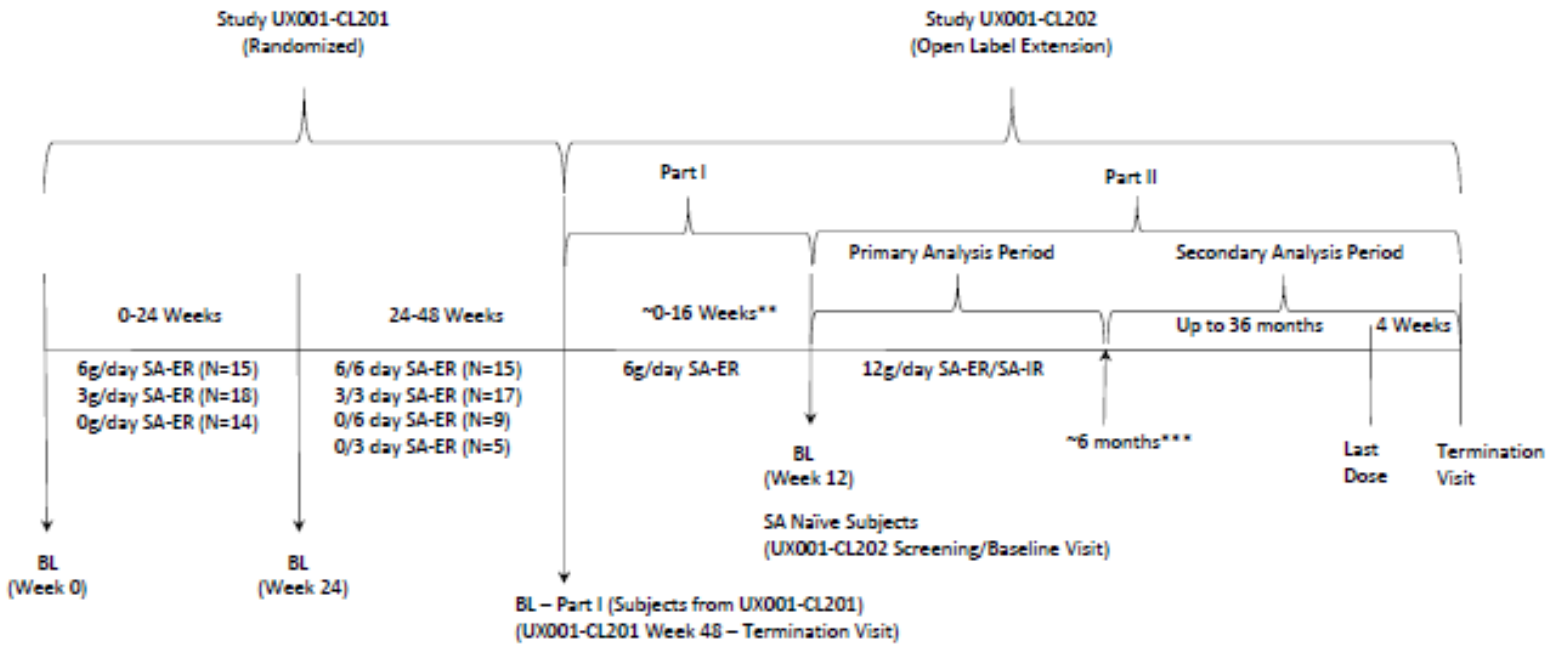
[g] Trough levels of free SA in serum; record the time of last dose and sample collection.

[h] Adverse Events will be collected after subject signs Informed Consent form.

[i] A one month supply of study drug will be dispensed at scheduled treatment visits; additional study drug will be shipped directly to subjects between visits on a monthly basis.

[j] Phone calls will be placed to each subject at least once between each study visit to assess treatment compliance with the dosing regimen. Additional telephone contacts with the subject may be placed as needed.

Figure 1 UX001-CL202 Study Periods and Analysis Map



** Participation in Part I varied by subject. The range of time for participation in Part I will be displayed by Subject in individual listings. Some Subjects who rolled over from UX001-CL201 went directly to Part II and the 12g/day SA-ER/SA-IR

*** Additional snapshots of data may be taken earlier and later for analysis.

4 ANALYSIS POPULATIONS

The following analysis populations are defined for this study:

Safety Population (SAFETY): All subjects who provide informed consent and receive at least one dose of planned study medication in either Part I or Part II of the study and provide any post-treatment safety information. The safety population may be further sub-divided into Part I-Safety Population and Part II-Safety Population where appropriate for planned summaries. Subjects included in the safety population will be analyzed as treated. The Safety Population will be the source for all planned safety endpoints and analyses.

Intent-to-Treat Population (ITT): All subjects who are in the Safety Population and provide a least one (1) post-baseline clinical endpoint (efficacy) assessment over the course of the study will be included in the ITT Population. The ITT population may be further sub-divided into Part I-ITT Population and Part II-ITT Population where appropriate for planned analyses. Subjects included in the ITT population will be analyzed as treated. The ITT population will be the source for all planned clinical endpoint (efficacy) assessments and analyses.

Treatment Naïve Population (TNP): Subjects who are identified and enrolled into Part II of the study as treatment naïve subjects will be included in this analysis population and analyzed as a separate subgroup.

5 ANALYSIS VARIABLES

Analysis variables will be required from both the UX001-CL201 study, carried over week 24 and week 48 analysis variables, as well as from UX001-CL202 from both Part I and Part II.

Additional variables may be added as this SAP is developed and/or as discussion unfolds concerning the usefulness of *derived* variables formulated using the information presented below.

5.1 Study Drug Dosing

Study Drug Dosing for the UX001-CL201 feeder study and for this study UX001-CL202 are mapped to present all possible treatment combinations that a subject may participate in within these two studies (Table 3).

Table 3 Study Drug Dosing Pathways: UX001-CL201 – UX001-CL202

	UX001-CL201		UX001-CL202	
Path	Weeks 0-24	Weeks 24-48	Part I	Part II
1	6g/day	6g/day	6g/day	12g/day
2	3g/day	3g/day	6g/day	12g/day
3	0g/day	6g/day	6g/day	12g/day
4	0g/day	3g/day	6g/day	12g/day
5	N/A	N/A	N/A	12g/day
The 0/6 and 0/3 treatment groups (pathways 3 and 4) may be combined during weeks 0-24 for UX001-CL201 subjects to form a placebo group for comparisons with pathway 5. The 0/6 and 6/6 treatment groups (pathways 1 and 3) and 0/3 and 3/3 treatment groups (pathways 2 and 4 may be combined to form 3g and 6g treatment groups for comparison with the 12g/day SA-ER/SA-IR dosing.				

A total of 5 separate treatment pathways are identified for evaluation. Subjects enrolled in UX001-CL202 who are members of the TNP will have no treatment pathway from the UX001-CL201 study. Subjects who roll over from UX001-CL201 into Part I of this study will continue on a dose of 6g/day SA-ER. These data will be used primarily for additional safety data. All subjects participating in Part II of this study will receive 12g/day SA-ER/SA-IR. The focus of the safety analyses for the primary objective will be on safety at the 6g/day SA-ER and safety at the 12g/day SA-ER/SA-IR doses.

5.2 Demographics and Baseline Characteristics

Demographic and Baseline Characteristics for the study population in UX001-CL202 will include the parameters listed in Table 4. For Subjects who roll over from the UX001-CL201 demographic parameters will be cross validated from the UX001-CL201 study into the UX001-CL202 study as the same variable.

Table 4 Demographic and Baseline Characteristic Variables

Analysis Variable Name	Analysis Variable Description	Code List/ Variable Notes
SEX	Subject Gender	M = Male, F = Female Will be carried over from UX001-CL201
AGE AGE1	Subject Age at time of Informed Consent – UX001-CL201 Subject Age at time of Informed Consent – UX001-CL202	Computed as (Date of Informed Consent – Date of Birth / 365.25) +1 For Subjects carried over from UX001-CL201 two ages will be reported: AGE and AGE1
RACE	Subject Race	1 = White, 2 = Black or African American, 3 = Asian, 4 = Native Hawaiian or Other Pacific Islander, 5 = American Indian or Alaska Native, 6 = Other (Specified). Will be carried over from UX001-CL201
ETHNIC	Subject Ethnicity	1 = Hispanic or Latino, 2 = Not Hispanic or Latino Will be carried over from UX001-CL201
HT	Subject Height at Baseline	Height in CM, assessed at baseline visit in UX001-CL202
WT	Subject Weight at Baseline	Weight in KG, assessed at baseline visit in UX001-CL202

Analysis Variable Name	Analysis Variable Description	Code List/ Variable Notes
BMI	Subject Body Mass Index (BMI) at baseline	Derived from baseline HT and Weight. Computed as WT (kg) / HT (m^2)
BMICAT	Subject BMI Category at baseline	Derived from BMI and assigned as: 1 = Underweight (<18.5) 2 = Normal weight (18.5–24.9) 3 = Overweight (25.0–29.9) 4 = Obese (30.0-39.9) 5 = Morbidly Obese (≥40.0)
Interval History	Analysis variables related to collection of HIBM interval history	Interval History data will be reported as collected by category.

5.3 Safety Variables

Safety analysis variables for the study population in UX001-CL202 will include the parameters listed in Table 5. Safety analysis variables will be summarized for Part I and Part II in this study. Baseline safety analysis variable values for subjects who roll over from UX001-CL201 will be the last safety variable assessment recorded in UX001-CL201. For subjects who are SA Naïve and enroll into Part II of this study the baseline value will be assigned as the screening visit for the subject.

Table 5 Safety Analysis Variables

Analysis Variable Name	Analysis Variable Description	Code List/ Variable Notes
Medical History: MHTERM MHDECOD MHPTCD MHBODSYS MHSOC MHSOCCD	 Verbatim MH Text Preferred MH Term Preferred Term Code Body System (SOC) Primary SOC Primary SOC Code	Will be carried over from UX001-CL201 for roll over subjects SA Naïve subjects will have baseline Medical History recorded at the screening visit Medical History will be coded with MEDDRA medical dictionary SOC and Preferred term. Medical history will be

Analysis Variable Name	Analysis Variable Description	Code List/ Variable Notes
		listed for all subjects participating in UX001-CL202
Physical Examination PE TERM PEDECOD	Verbatim PE Text Preferred PE Term	Physical Examination data will be reported as collected by term.
Neurological Examination NE TERM NEDECOD	Verbatim NE Text Preferred NE Term	Neurological Examination data will be reported as collected by term.
Concomitant medications: CMTRT CMDECOD PREFCODE DCL2C	Verbatim CM Text Preferred CM Term Preferred Code ATC Level 2 Code	Concomitant Medications will be coded with WHODRUG medications dictionary to primary term and ATC Level 2 code. Concomitant Medications will be listed for all subjects participating in UX001-CL202
Adverse Events AETERM AEDECOD AEPTCD AEBODSYS AESOC AESOCCD AESEV AECTCAE	Verbatim AE Text Preferred AE Term Preferred Term Code Body System (SOC) Primary SOC Primary SOC Code AE Severity Code CTCAE Severity Grade	Adverse Events will be assessed on a continual basis during the conduct of the trial. Adverse Events will be coded with MEDDRA medical dictionary SOC and Preferred term
Vital Signs: SYSBP DIABP HR RP TEMP	Systolic BP(mmHg) Diastolic BP (mmHg) Heart Rate (bpm) Respiratory Rate (bpm) Temperature (°C)	Vital Signs will be assessed at baseline and at subsequent visits over the course of the study. Baseline will be carried over for UX001-CL201

Analysis Variable Name	Analysis Variable Description	Code List/ Variable Notes
		roll-over subjects from the last visit in UX001-CL201.
Laboratory Studies: LBCAT=HEMA HB MCHC MCHB MCV PLATLET RBC RETIC WBCDIFF NEUTABS NEUTPCT LYMPABS LYMPPCT EOSINABS EOSINPCT BASOABS BASOPCT WBC	 Hemoglobin (Hb) MCH Concentration Mean Corpuscular Hb Mean Corpuscular Vol Platelet Count Red Blood Cell Count Reticulocyte Count WBC Differential Neutrophil count (abs) Neutrophil count (%) Lymphocyte count (abs) Lymphocyte count (%) Eosinophil count (abs) Eosinophil count (%) Basophil count (abs) Basophil count (%) White Blood Cell	Laboratory data will be identified stored by category (LBCAT) and test code (LBTESTCD). Units standardized across the study.
Laboratory Studies: LBCAT=CHEM ALTSGPT ALKP AMY ASTSGOT BILID BILIT BUN CALC CHLOR CHOLT CK	 Alanine aminotransferase Alkaline phosphatase Amylase Aspartate aminotransferase Bilirubin (direct) Bilirubin (total) Blood urea nitrogen Calcium Chloride Cholesterol (total) Creatine kinase (CK)	Laboratory data will be identified stored by category (LBCAT) and test code (LBTESTCD). Units standardized across the study.

Analysis Variable Name	Analysis Variable Description	Code List/ Variable Notes
CREAT GGT GLUC LDH LIP PHOS K ALB ALBT TRIG	Creatinine Gamma-glutamyl transpeptidase Glucose Lactate dehydrogenase Lipase Phosphorus Potassium Protein (ALB) Protein (Total) Triglycerides	
Laboratory Studies: LBCAT=URINE COLOR PH SG KET PROTEIN GLUC BILI NIT UROB HEMO CREAT	 Color pH Specific Gravity Ketones Protein Glucose Bilirubin Nitrate Urobilinogen Hemoglobin Creatinine	Laboratory data will be identified stored by category (LBCAT) and test code (LBTESTCD). Units standardized across the study.
Laboratory Studies: LBCAT=SPEC FSACID PREGS PREGU	 Free serum SA Serum Pregnancy Urine Pregnancy	Laboratory data will be identified stored by category (LBCAT) and test code (LBTESTCD). Units standardized across the study.

5.4 Efficacy Variables

Efficacy analysis variables for the study population in UX001-CL202 will include the parameters listed in Table 6. Efficacy analysis variables will be summarized for Part II in this study to gain a better understanding of the 12 g/day SA-IR dose. Baseline efficacy analysis

variable values for subjects who roll over from UX001-CL201 will be identified based on the requested analysis. Multiple baselines will be used to evaluate the change in disease course over the treatment pathways (Table 3). The baseline value to be used for the change from baseline comparisons will be identified with the specific analyses described in this SAP.

Clinical efficacy analyses to be completed may include the following for the analysis variables listed below:

(1) Muscle strength as measured by HHD UE, LE and individual components, and reported as force in kg and percent of predicted normal,

(2) Walking ability as measured by the 6MWT, and reported as distance in meters and percent of predicted normal,

(3) Walking speed as measured by the walking speed test, which will be reported in seconds and percent of predicted normal for each walking speed, comfortable and maximum,

(4) Arm raising ability as measured by the weighted arm lift test, which will be reported as the total number of completed repetitions.

(5) Functional disability as measured by the HIBM-FAS, which will be reported as a total score and subscale scores for mobility, self-care, and upper extremity function with lower scores associated with greater disability.

Table 6 Efficacy Analysis Variables

Analysis Variable Name	Analysis Variable Description	Code List/ Variable Notes
Hand Held Dynamometry: LELBEXT LELBFLX LGRIP LHIPABD LHIPADD LHIPEXT LHIPFLX LKEY LKNEEXT LKNEFLX LPALMAR LSHLDABD	 Left Elbow Extension (kg) Left Elbow Flexion (kg) Left Grip (kg) Left Hip Abduction (kg) Left Hip Adduction Left Hip Extension (kg) Left Hip Flexion (kg) Left Key (kg) Left Knee Extension (kg) Left Knee Flexion (kg) Left Palmar (kg) Left Shoulder Abduction (kg)	Muscle strength based on the maximum voluntary isometric contraction (MVIC) against a hand-held dynamometer will be measured in the following muscle groups: gross grip, pinch, shoulder abductors, elbow flexors, elbow extensors, hip abductors, hip

Analysis Variable Name	Analysis Variable Description	Code List/ Variable Notes
LTIP RELBEXT RELBFLX RGRIP RHIPABD RHIPADD RHIPEXT RHIPFLX RKEY RKNEEXT RKNEFLX RPALMAR RSHLDABD RTIP HHDHECS HHDLECS	Left Tip (kg) Right Elbow Extension (kg) Right Elbow Flexion (kg) Right Grip (kg) Right Hip Abduction (kg) Right Hip Adduction Right Hip Extension (kg) Right Hip Flexion (kg) Right Key (kg) Right Knee Extension (kg) Right Knee Flexion (kg) Right Palmar (kg) Right Shoulder Abduction (kg) Right Tip (kg) HHD Upper Extremity CS HHB Lower Extremity CS	adductors, hip flexors, hip extensors, knee flexors and knee extensors. The total force (kg) will be measured as well as the percent of predicted normal force based on age, gender, height and weight (where applicable).
Six-Minute Walk Test: SXMWTDIS SXMWTPP	 6-Min Walk Test (meters) 6-Min Walk Test (%pred)	The total distance walked (meters) in a six minute period will be measured as well as the percent of predicted normal distance based on age and gender.
Walking Speed Test: COMFWALK MAXWALK	 Comfortable Gait Speed (cm/s) Maximum Walk Speed (cm/s)	The time required to walk 25 feet (7.62 meters) will be assessed at a comfortable and a maximum gait speed. The total number of seconds required for each speed will be recorded. Individual subject performance will also be compared to healthy peers based

Analysis Variable Name	Analysis Variable Description	Code List/ Variable Notes
		on normative data.
Weighted Arm Lift Test LNUMLIFT RNUMLIFT	 Left Arm Number of Lifts Right Arm Number of Lifts	The number of times the subject can raise a 1 kg weight above the head in a 30-second period will be recorded. The test will be performed bilaterally.
HIBM Functional Activities Scale FATSCR MOBLSCR SCARESCR UESCR	 Functional Activity Total Score Mobility Score Self-Care Score Upper Extremity Score	The total score, as well as subscale scores for mobility, self-care, and upper extremity function on an interview-administered functional disability measure will be recorded.

5.5 Exploratory Efficacy Variables

Exploratory Efficacy analysis variables for the study population in UX001-CL202 will include the parameters listed in Table 7. These Exploratory Efficacy analysis variables will be summarized for both Part I and Part II in this study to gain a better understanding of the 6 g/day SA-ER and 12 g/day SA-IR doses.

Table 7 Exploratory Efficacy Analysis Variables

Analysis Variable Name	Analysis Variable Description	Code List/ Variable Notes
Laboratory Studies: LBCAT=CHEM CK SA	 Creatine Kinase (u/L) Sialic Acid	Biomarkers

Analysis Variable Name	Analysis Variable Description	Code List/ Variable Notes

6 STATISTICAL METHODOLOGY

6.1 Sample Size

Approximately 46 subjects may be enrolled in Part I of this open-label extension study. Sample size is limited to the number of subjects enrolled in the Phase 2 safety and efficacy study, UX001-CL201, who achieve at least 80% treatment compliance and study visit completion. As Part I of the study is intended to evaluate the long-term safety of 6g/day SA-ER in subjects with GNE Myopathy and ascertain the long-term effect of SA-ER treatment on muscle strength, mobility, and functional disability, the sample size is deemed reasonable to satisfy Part I study objectives.

An additional 10 subjects will be enrolled into Part II of the study. This subset of treatment naïve GNE Myopathy subjects will provide additional safety and efficacy information following treatment with SA-ER/SA-IR. Note that more than 10 planned subjects may be enrolled in this subset of treatment naïve GNE Myopathy subjects, as new subjects are identified at the study centers. These additional subjects will only add additional information and informative value to this treatment naïve GNE Myopathy population. No modifications of updates to the SAP are needed for additional subjects in this group.

The study design is open-label with all subjects receiving the same treatment. Therefore, the study is not powered to assess statistically significant comparisons. Instead, the sample size is intended to provide the maximum amount of long-term safety and efficacy data for the investigational product.

6.2 Randomization

This is an Open-Label Study where all subjects who roll over from study UX001-CL201 will receive 6g/day SA-ER in Part I and 12g/day SA-ER/SA-IR in Part II. Subjects enrolled into this study who are treatment naïve GNE Myopathy subjects will be included in Part II and receive 12g/day SA-ER/SA-IR. Since all subjects will receive the same treatment in Part II, randomization or blinding of study drug is not necessary. No randomization schedule or stratification strategy at baseline was developed for this study.

6.3 Analysis at 6-months (Part II)

An analysis will be conducted following 6 months of treatment with 12g/day SA-ER/SA-IR in Part II of the study. This analysis will be the primary analysis for the study for clinical efficacy information and initial safety information.

This analysis will be completed with the SAFETY, ITT, and TNP populations.

The independent DMC may review the safety information from the analysis to assess the impact on the safety of the participants or the ethics of the study. The DMC may also make other recommendations to Ultragenyx Pharmaceutical concerning continuation, termination or other modifications of the study based on their observations of the study at the analysis or other DMC scheduled review of study data.

Ultragenyx Pharmaceutical may also at its discretion complete additional examinations at additional time points for trends in efficacy and safety parameters after the analysis at 6-months (Part II) has been completed to monitor and assess the 12g/day SA-ER/SA-IR dose.

6.4 Final Analysis at end of Part II.

After all subjects have completed Part II dosing and follow-up termination visit on the 12g/day SA-ER/SA-IR dose at approximately 36 months, the database will be locked and final analyses will be completed.

6.5 General Considerations for Statistical Analysis

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 tables as <0.0001.

There will be no multiplicity adjustments, or adjustments for multiple comparisons.

Descriptive summaries of variables will be provided where appropriate. For continuous variables, the number of non-missing values (n) and the median, mean, standard deviation, minimum, and maximum will be tabulated by treatment. For categorical variables, the counts and proportions of each value will be tabulated by treatment. Expansion of descriptive table categories within each treatment may occur if such elaborations are thought to be useful.

All collected data 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, additional analyses identified after planned analyses are completed. Likewise, the list of planned tables (Section 8.1) is the list of planned tables prospectively defined for the study analyses. Additional tables and figures may be defined to further evaluate study results and the SAP will not be amended to list these additional analysis tables.

6.5.1 Changes in Analysis in Comparison to Study Protocol

The analyses described in this analysis plan are consistent with the intended analyses described in the study protocol. In addition results from the UX001-CL201 study, both the Week 24 and Week 48 analyses, will be utilized as baseline information to explore and compare the various dosing combinations and trends in efficacy parameters, between the UX001-CL201 randomized feeder study and the UX001-CL202 extension study.

6.5.2 Derived Efficacy Variables

Muscle Strength - Hand Held Dynamometry (HHD):

HHD Upper Extremity (UE) composite score is calculated as the sum of the average of the right and left raw scores (as measured in kg) for the following muscle groups: grip, shoulder abductors, elbow flexors and elbow extensors. 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.

HHD Lower Extremity (LE) composite score is calculated as the sum of the average of the right and left raw scores (as measured in kg) for the following muscle groups: hip flexors, hip extensors, hip abductors, hip adductors and knee flexors. Knee extensors will not be included in the calculation of the LE HHD composite score. 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 strength values from bilateral pinch (tip, key and palmar), grip, shoulder abductors, elbow flexors, elbow extensors, hip flexors, hip extensors, hip abductors, hip adductors, knee flexors and knee extensors collected at baseline using the regression equations generated for the variables. Baseline predicted normal values will be used to derive % of predicted normal values for all future study time points throughout the study.

% of predicted normal HHD values for the individual muscle groups will be calculated as follows: [(Raw strength value/Predicted normal strength value) *100].

Patient Reported Outcomes:

HIBM Functional Activities Scale (HIBM-FAS) Total Score will be calculated as the sum of the Total Scores range from 0 to 100 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 range from 0 to 40 with higher scores representing greater mobility. Upper Extremity subscale scores range from 0 to 32 with higher scores representing more skilled, independent use of the arms during functional

activity performance. Self-Care subscale scores range from 0 to 28 with higher scores representing greater independence with functional care activities.

6.5.3 Derived Safety, Dosing, and Medication Variables

Non Treatment Emergent Adverse Events (AEs) include all adverse events that stopped the day prior to the start of study medication, started prior to the start of study medication but did not increase in severity or relationship during treatment, or started more than 30 days after the final study medication dosing date. In this study there is no expectation on non-treatment emergent adverse events in any subjects who roll-over from UX0010-CL201. Subjects in the treatment naïve population may have non-treatment emergent adverse events recorded if an event occurs between screening (informed consent) and the first dose of planned study medication (12g.day SA-ER/SA-IR).

Treatment Emergent Adverse Events (TEAE) include all adverse events that start on or after the first dose of study medication, or adverse events that are present prior to the first dose of study medication, but their severity or relationship increases after the first dose of study medication up to and including 30 days after the final study medication dosing date.

Dosing: Number of doses administered will be calculated for each subject by summing the number of doses administered over all visits.

Medications:
Prior medications include all medications that are taken prior to the first dose of study medication date.

Concomitant medications include all medications that are taken on or after the date of first dose of study medication.

6.5.4 Data Handling

Unscheduled or repeated laboratory results will not be analyzed for the summary of continuous values but may be included in any post-hoc laboratory shift tables as follows. Unscheduled tests will be included with the time of the nearest regularly scheduled test. If there is a scheduled laboratory result and one or more unscheduled tests assigned to the same time point, the most conservative test (i.e., a test with low or high results) will be used. Repeated tests will be included only if they reflect abnormal (low or high) results and the corresponding original results are normal.

6.5.5 Handling of Early Termination Visits

Early termination visit data for safety variables will be analyzed at the closest scheduled visit. If the closest visit has valid data, the early termination data will be assigned to the next available visit.

6.5.6 Handling of Missing Values

Partial or Missing Dates

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.

A. Start Dates

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

2) If the month is unknown, then:

i) If the year matches the first dose date year, then impute the month and day of the first dose date.

ii) Otherwise, assign 'January'

3) If the day is unknown, then:

i) If the month and year match the first dose date month and year, then impute the day of the first dose date.

ii) Otherwise, assign the first day of the month.

B. Stop Dates

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

2) If the month is unknown, then assign 'December.'

3) If the day is unknown, then assign the last day of the month.

Imputation of missing endpoint assessments:

Observed cases with data missing at random will be assumed for all planned analyses. If missing endpoint assessments are observed then the last observed value, at the collected time point, will be included in planned analyses.

Following a data review at the 6-month interim analysis and at the completion of the study Ultragenyx Pharmaceutical may at their discretion define an imputation rule if missing data for efficacy assessment and endpoints is believed to be non-random, and has some aspect of systematic error associated with the missing data. If this is determined following data review then a Last Observation Carried Forward (LOCF), or Baseline Observation Carried Forward (BOCF) may be considered for imputation for missing endpoint efficacy data.

Imputation of missing endpoint assessments for HHD measures:

Missing values explained as "**Too Weak**" are to be converted to zero scores for all HHD measures including Grip, Tip Pinch, Key Pinch, Palmar Pinch, Shoulder Abduction, Elbow Flexion, Elbow Extension, Knee Flexion, Knee Extension, Hip Flexion, Hip Extension, Hip Abduction and Hip Adduction.

6.5.7 Pooling of Investigator Centers

The data from all study centers will be pooled together for the primary analyses. No *a priori* pooling strategy will be defined for this study. If after review of study data prior to planned interim analyses and final analyses the data review meeting identifies cohorts of sites that warrant pooling then a pooling strategy will be defined and implemented, and presented in the final CSR.

6.5.8 Determination of Baseline Values

Multiple baseline values for efficacy endpoints will be considered for the planned analyses. Figure 1 presents an analysis map that highlights the various possible baselines for planned analyses. Table 3 presents a dosing pathway matrix for all subjects enrolled in the study. Each pathway can be associated with a different baseline for analysis summaries and comparisons.

In order the examine the long term trends and changes in SA therapy for those subjects who roll-over from UX001-CL201 additional analyses will also be performed using baseline assessments obtained at the following time points (Figure 1):

- UX001-CL201 6/6 and 3/3 rollover subjects: UX001-CL201 Week 0 Visit
- UX001-CL201 0/6 and 0/3 rollover subjects: UX001-CL201 Week 24 Visit
- UX001-CL201 0/6 + 6/6 rollover subjects: UX001-CL201 Week 48 Visit
- UX001-CL201 0/3 + 3/3 rollover subjects: UX001-CL201 Week 48 Visit
- UX001-CL201 All rollover subjects: UX001-CL201 Week 48 Visit

- UX001-CL201 All rollover subjects: UX001-CL202 Part I Termination Visit

- UX001-CL202 Treatment Naïve Subjects: UX001-CL202 Part II Screening/Baseline Visit (Week 0: Note that protocol refers to this as week 12 on the T&E schedule.)

6.5.9 Coding of Events and Medications

Adverse events will be coded to standardize presentation of AEs and TEAEs. AEs will be mapped to the Medical Dictionary for Regulatory Activities (MedDRA Version 11.1) system for reporting (preferred term and body system).

Concomitant medications will be coded using WHO-DD (Drug Dictionary) (Version 2009003).

6.5.10 Analysis Software

Data manipulation, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will be performed primarily using SAS (release 9.1.3 or higher) for Windows. If the use of other software is warranted, the final clinical study report will detail what software was used and for what purposes.

6.5.11 Analysis Data Sets

Analysis data sets will be developed for all study data in UX001-CL202. The analysis data sets will conform as close as possible to the CDISC Analysis Data Model (ADaM). Because this study also utilizes analysis data from the feeder study UX001-CL201 the final analysis data sets from this study will also be utilized to build, where appropriate, pooled analysis data sets with UX001-CL202. Subjects who roll over from the UX001-CL201 study into UX001-CL202 will carry with them the same USUBJID (Subject identifier) from UX001-CL201 for continuity of analysis data between studies.

6.6 Statistical Analysis: Disposition, Dosing, and Baseline Characteristics

6.6.1 Subject Disposition

The tabulation of number of subjects in each treatment group in both Part I (6g/day SA-ER) and Part II (12g/day SA-ER/SA-IR) and overall will be displayed for all subjects who are screened (Treatment Naïve Subjects: Part II), roll-over from UX001-CL201, in the Safety Population, and in the ITT Population, respectively.

The number and percent of subjects who completed or discontinued the study (at both the interim analysis and final analysis) will be displayed for each treatment group and overall together with reasons for early termination, where the percent is with respect to the total number of randomized subjects in that treatment group.

6.6.2 Dosing Summary

The number of doses administered will be summarized by treatment group for both the Safety and ITT Populations. Study medication dispensing and treatment compliance will be summarized in individual subject listings.

6.6.3 Demographics and Baseline Characteristics

Subject demographic data and baseline characteristics will be summarized descriptively by treatment group and overall. The demographic data and baseline characteristics will be summarized for both the Safety and ITT Populations.

Inclusion and Exclusion criteria will be presented in a listing.

6.6.4 Prior and Concomitant Medications

Concomitant medications will be assessed at all visits and throughout the course of the study.

Prior Medications: The number and percent of prior medications recorded for Treatment Naïve Subjects (enrolled directly into Part II) will be presented by the ATC class and preferred term as coded in the WHO-Drug dictionary (WHO-DD, version 200903). Prior medications will not be summarized for subjects who roll-over from UX001-CL201.

The number and percent of Concomitant Medications recorded for all subjects will be summarized by treatment group in Part I (6g/day SA-ER) and Part II (12g/day SA-ER/SA-IR) by the ATC class and preferred term as coded in the WHO-Drug dictionary.

Prior and concomitant medications will be summarized for the Safety Population.

6.7 Statistical Analysis: Clinical Efficacy

6.7.1 Planned Comparisons for Clinical Efficacy Parameters

The planned comparisons for UX001-CL202 are based on change from baseline assessments, where different baselines are utilized to evaluate treatment across a subject's treatment in

both UX001-CL201 and UX001-CL202. Table 8 presents the planned comparisons for study data obtained in UX001-CL202 compared with study data from UX001-CL201 for roll-over subjects, as well as the treatment naïve subjects in UX001-CL202.

Clinical efficacy data collected in Part I of UX001-CL202 (all roll-over subjects dosed with 6g/day SA-ER) will not be included in planned comparisons for the clinical efficacy analysis.

Additional comparisons not specified in this statistical analysis plan may be completed as prospective analyses are completed to better understand study results. These additional comparisons will be clearly identified in final reporting.

Table 8 Planned Comparisons

Planned Comparison	Description
Primary Analysis #1: Week 24 12g/day SA/ER/SA-IR vs. Week 0	All subjects who roll-over from UX001CL201 will have their week 0 assigned as baseline (Part I termination visit of the 202 study) and the change from this score will be compared to the week 24 12g/day SA-ER/SA-IR treatment to assess the impact of the 12g/day SA-ER/SA-IR dose.
Primary Analysis #2: Week 24 12g/day SA/ER/SA-IR vs. Week 48 UX001-CL201 for 6/6+0/6 SA-ER	All subjects who roll-over from UX001CL201 will have their week 48 assigned as baseline and the change from this score will be compared to the week 24 12g/day SA-ER/SA-IR treatment to assess the impact of the 12g/day SA-ER/SA-IR dose across the combined 6/6+0/6 dose (UX001-CL201 subjects treated with 0/6 or 6/6 SA-ER will be combined for comparison from dosing pathways 1 and 3 from Table 3). A second comparison will be with a 6 minute walk test at Screening of >=200 m (6MWT>=200m)
Primary Analysis #3: Week 24 12g/day SA/ER/SA-IR vs. Week 48 UX001-CL201 for 3/3+0/3	All subjects who roll-over from UX001CL201 will have their week 48 assigned as baseline and

Planned Comparison	Description
SA-ER	the change from this score will be compared to the week 24 12g/day SA-ER/SA-IR treatment to assess the impact of the 12g/day SA-ER/SA-IR dose across the combined 3/3+0/3 dose (UX001-CL201 subjects treated with 0/3 or 3/3 SA-ER will be combined for comparison from dosing pathways 2 and 4 from Table 3) A second comparison will be with a 6 minute walk test at Screening of >=200 m (6MWT>=200m)
Secondary Analysis: Stability in endpoint over time and dose from Week 0 UX001-CL201 through Week 24 UX001-CL202. (Trend over time)	All subjects who roll-over from UX001CL201 will have their week 0 assigned as baseline and the stability from this baseline score will be assessed over time through the week 24 12g/day SA-ER/SA-IR treatment to assess the impact of dose combinations over time. For this analysis the UX001-CL201 subjects treated with 0/6 or 6/6 SA-ER will be combined for analysis from dosing pathways 1 and 3 and subjects treated with 0/3 or 3/3 SA-ER will be combined for analysis from dosing pathways 2 and 4 (Table 3). Each dosing pathway combination will be a separate analysis to assess the trend in endpoint scores over time and dose. A second comparison will be with a 6 minute walk test at Screening of >=200 m (6MWT>=200m)
Treatment Naïve Primary Analysis: Week 24 12g/day SA/ER/SA-IR vs. Week 0 Baseline (Week 12 on T&E)	Treatment Naïve subjects who enroll in UX001-CL202 will have a primary comparison of their change from baseline assessment for efficacy parameters.
Treatment Naïve Secondary Analysis: Week 24 12g/day SA/ER/SA-IR vs.	Treatment Naïve subjects in UX001-CL202

Planned Comparison	Description
Week 0-24 UX001-CL201 Placebo	endpoint data from week 0 to 24 will be compared to the UX001-CL201 Placebo (for those patients with 6MWT >=200m) treated subjects' endpoint data from week 0 to 24 for change from baseline assessments.

Additional comparisons may be defined upon review of the data to examine trends throughout a subject's treatment course through both UX001-CL201 and UX001-CL202, via the dosing pathways identified in Table 3 and Figure 1.

6.7.2 Statistical Modeling: Repeated Measure Model: General Estimating Equations (GEE)

The primary analysis method to be applied for all repeated measures efficacy parameters will be a general estimating equation (GEE) model (Hanley 2003, SAS Software 2010). A generalized estimating equation (GEE) procedure will be performed for the repeated measures associated with the clinical efficacy endpoints analysis and associated planned comparisons.

The GEE regression model is of the general form:

$$Y_{ij} = \alpha + \beta_1 X_{1i} + \ldots + \beta_n X_{yi} + \beta_{n1} T_{1ij} + \ldots + \beta_{nx} T_{xij}\, X_{xi} + \varepsilon_{ij}$$

Where, we assume that the Y_{ij} follow a Normal distribution with $\text{var}(Y_{ij}) = \sigma^2$, and $\text{cov}(Y_{ij}, Y_{ik}) = \delta$ (exchangeable correlation). It follows that the link function is the identity. The model above has been parameterized with reference cell coding, where the coefficient estimates corresponding to the treatment variables (X_2, X_3) capture the mean differences in the change from baseline for the planned comparison. The model will provide that a test of change from baseline at the planned time points (identified in the comparisons in Table 8) is the linear estimate of $\beta_3 + \beta_{12}$. The following general form and sample SAS Software program code provides an example of this type of GEE model implementation across the planned efficacy parameters described in Table 6 and Table 7:

```
PROC GENMOD DATA=<data set name>;
    CLASS <id variable>;
    MODEL <efficacy parameter> = <trt1>  <trt2>  <baseline>
              <covariates> <vx_trt1>  <vx_trt2>  <interactions> / DIST=NORMAL;
    REPEATED SUBJECT=<id> / CORR=CS;
    ESTIMATE '<planned comparison>'  <trt1> 1 <trt2> 1  <vx_trt1>  1;
```

RUN;
QUIT;

where:
<id variable> uniquely identifies the subject: A record for every visit for each subject,
<efficacy parameter> identifies the clinical efficacy parameter of interest,
<baseline> identifies the baseline for the efficacy parameter measure for the subject,
<planned comparison> comparisons identified in Table 8,
<trt1> is the 12g/day SA-ER/SA-IR variable (1,0),
<trt2> is the defined dose for comparisons (1,0),
<vx> are coded (0,1) visit variables,
<vx_trt1>, <vx_trt2> are coded (0,1) visit x treatment interaction variables,
<covariates> define any additional baseline covariates assessed for inclusion in the GEE model at $p<0.05$.

In general, baseline value, gender, and age will be covariates in the GEE models for each planned analysis where appropriate. The final form of the GEE model for each clinical efficacy parameter and planned comparison will be described in the final study report.

6.7.3 Statistical Modeling: Analysis of Covariance (ANCOVA)

Where appropriate, supportive analyses of clinical efficacy parameters may be completed with Analysis of Covariance (ANCOVA) (Kutner 2005). ANCOVA combines features of both analysis of variance (ANOVA) and regression. It augments the ANOVA model with one or more additional quantitative covariates, which are related to the response variable. The covariates are included to reduce the variance in the error terms and provide more precise measurement of the treatment effects. ANCOVA is used to test the main and interaction effects of the factors, while controlling for the effects of the covariate. In the analyses of this study, ANCOVA will be used for the variables that were measured at the baselines identified in Figure 1. ANCOVA may be implemented to assess treatment group differences in comparisons identified in Table 8 while controlling for the screening measure of the clinical efficacy variable being analyzed. ANCOVA may be utilized where repeated measures are not anticipated for a planned, supplemental analysis or in cases where further understanding of study results will benefit from the use of ANCOVA.

6.7.4 Statistical Modeling: Graphic Displays of Study Results

Graphical displays of study endpoints will be completed and include both observed study data and modeled analyses. Arithmetic means, Least Square Means (LS Means), LS means differences, and appropriate measure of dispersion (e.g. standard deviation, standard error) or confidence intervals may be display in figures to augment the modeled analysis. In general,

graphical displays will be accompany each planned analysis to present study results, utilizing companion numbering aligned with tabular numbering.

Scatter points over the observation time intervals for UX001-CL201 through the 6-month (24 week) time point for UX001-CL202 will be completed for each study endpoint, by treatment pathway (Table 3), to examine trends in results over time of treatments for subjects who roll-over from UX001-CL201. Treatment Naïve subjects enrolled in Part II of UX001-CL202 will have the scatter plots scaled for their participation with treatment 12g/day SA-ER/SA-IR. In general the scatterplots will include, for any given endpoint, all observations for every subject presented in a single figure, color coded for treatment pathways.

Bar charts will be completed for each endpoint where change from baseline is examined and treatment differences are evaluated. Either the mean change or LS Mean's differences, whichever is appropriate for the endpoint, will be displayed to support the statistical analyses performed.

Exploratory scatter plots, and correlations, will be completed to examine study endpoint means (or LS means) compared to Free Sialic Acid (SA), and other serum biomarkers of interest, to explore the treatment effects with the 12g/day SA-ER/SA-IR dose compared to previous doses subjects (Table 3).

6.7.5 Efficacy Analysis: Muscle Strength - Hand Held Dynamometry (HHD)

The hand held dynamometry (HHD) assessment is completed in UX001-CL202 at the Part II time points of Screening/Baseline (last visit in Part I), months 3, 6, 12, 18, 24, 30, 36, and the termination visit (Table 2). The HHD parameters will be summarized into composite scores and GEE analyses will be performed.

HHD Upper Extremity (UE) Composite Score

HHD UE composite scores will be used to evaluate change in upper extremity muscle strength. HHD UE composite scores achieved for the 12g/day SA-ER/SA-IR dosing group at each study time point will be evaluated using descriptive statistics.

A GEE model (see Section 6.7.2) will be completed for the week 24 (6 month) analysis and will include the visits from Part II of UX001-CL202 (Months 1 to 6) accounting for time on the 12g/day SA-ER/SA-IR treatment with subjects who cross-over from treatment administered in UX001-CL201 (Table 3). The primary model will incorporate the treatment groups defined in the planned comparisons (Table 8).

HHD Lower Extremity (LE) Composite Score

HHD LE composite scores will be used to evaluate change in lower extremity muscle strength. HHD LE composite scores achieved for the 12g/day SA-ER/SA-IR dosing group at each study time point will be evaluated using descriptive statistics. The same modelling strategy applied for the HHD UE will be applied for the HHD LE Composite score.

6.7.6 Exploratory Efficacy Analysis: Hand Held Dynamometry (HHD)

HHD Individual Raw Strength Scores

Strength in the individual muscle groups tested by HHD will be assessed using raw scores (as measured in kg) from the right and left sides. Individual muscle groups to be assessed in the upper extremities include pinch (key, tip and palmar), gross grip, shoulder abductors, elbow flexors and elbow extensors. Individual muscle groups to be assessed in the lower extremities include hip abductors, hip adductors, hip flexors, hip extensors, knee flexors and knee extensors.

Raw strength scores achieved for the 12g/day SA-ER/SA-IR treatment group in UX001-CL202 at the Part II time points of Screening/Baseline (last visit in Part I), months 3, 6, 12, 18, 24, 30, 36, and the termination visit (Table 2) will be evaluated for the average of the right and left sides of the individual muscle groups using descriptive statistics. If one side is missing, it will be imputed using the other side.

A GEE model (see Section 6.7.2) will be completed for the week 24 (6 month) primary analysis and will include the visits from Part II of UX001-CL202 (Months 1 to 6) accounting for time on the 12g/day SA-ER/SA-IR treatment with subjects who cross-over from treatment administered in UX001-CL201 (Table 3). The GEE model will incorporate the treatment groups defined in the planned comparisons (Table 8) for raw strength scores.

HHD % Predicted Normal Strength Scores

Strength in the individual muscle groups tested by HHD will be assessed using % of predicted normal scores for the right and left sides. Predicted normal values will be calculated as described in Section 6.5.2. Individual muscle groups to be assessed in the upper extremities include pinch (key, tip and palmar), gross grip, shoulder abductors, elbow flexors and elbow extensors. Individual muscle groups to be assessed in the lower extremities include hip abductors, hip adductors, hip flexors, hip extensors, knee flexors and knee extensors.

Percent of predicted normal scores achieved for the 12g/day SA-ER/SA-IR treatment group in UX001-CL202 at the Part II time points of Screening/Baseline (last visit in Part I), months 3, 6, 12, 18, 24, 30, 36, and the termination visit (Table 2) will be evaluated for the average of the right and left sides of the individual muscle groups using descriptive statistics.

A GEE model (see Section 6.7.2) will be completed for the week 24 (6 month) primary analysis will include the visits from in Part II of UX001-CL202 (Months 1 to 6) accounting for time on the 12g/day SA-ER/SA-IR treatment with subjects who cross-over from treatment administered in UX001-CL201 (Table 3). The GEE model will incorporate the treatment groups defined in the planned comparisons (Table 8) for HHD % predicted normal strength scores.

Additional Analyses: HHD UE, LE Scores

In addition to the above analyses, additional analyses will be conducted to help further assess both the degree of change over the time course of treatment in both UX001-CL201 and in UX001-CL202 and the effect of crossover from the dosing pathways (Table 3). For each of the treatment pathway groups (or combinations thereof) the HHD UE and LE composite change over time will be evaluated to seek understanding on the various dosing pathways and the effect of the 12g/day SA-ER/SA-IR dosing.

The cross-over treatment pathway groups may be compared with the change observed in prior treatment period HHD UE and LE scores. Trends in the change observed in each parameter will be displayed using graphical techniques. These latter analyses will help evaluate an effect of SA over an extended period of time from UX001-CL201 through UX001-CL202, as well as on the reversal of HHD change for subjects that may have declined during the placebo period (Weeks 0-24 in UX001-CL201). These analyses will help to understand the long term impact of treatment over dosing pathways and assess whether the rate of change in individual subjects has changed significantly from before to after the various treatments received.

Additional Analyses: Serum SA Levels and HHD UE, LE Scores

An analysis of change in mean serum SA level impact on HHD UE, LE scores will be performed. Changes in mean serum SA level observed during the cross-over treatment pathway groups may be compared with the change observed in prior treatment period HHD UE and LE scores. Trends in these changes in observed SA levels and HHD UE and LE scores will be displayed using graphical techniques.

Subjects achieving a mean change in serum SA of 0.1 mg/dl or greater over their individual baseline over all visits may be compared to those subjects with <0.1 mg/dl mean change in SA level. Subjects will be placed into either the 0.1 mg/dl or greater mean difference group or the less than 0.1 mg/dl mean difference group, and then the change in HHD UE and LE scores will be compared across these two groups using a GEE model.

6.7.7 Efficacy Analysis: Six-Minute Walk Test Distance

The Six Minute Walk Test (6MWT) will be used to evaluate change in walking capacity. 6MWT distance observed for the 12 g/day SA-ER/SA-IR treatment group will be summarized using descriptive statistics at each time point from Part II of UX001-CL202 (Table 2).

A GEE analysis model will be developed to examine the change in 6MWT distance for the 6-month part II analysis with study time points as categorical predictors and age, gender and Screening 6MWT distance as covariates. The defined baselines and planned comparisons to be examined in this analysis are identified in Table 8.

In addition the cross-over treatment pathway groups may be compared with the change observed in prior treatment period for the 6MWT. Trends in the change observed in 6MWT will be displayed using graphical techniques.

6.7.8 Exploratory Efficacy Analysis: 6MWT

% Predicted of Normal 6MWT Distance

The 6MWT performance of subjects relative to peers will be evaluated as a sensitivity analysis using % of predicted normal 6MWT distance values. Predicted normal values will be calculated as described in section 6.5.2. Percent of predicted normal 6MWT distance achieved for the 12g/day SA-ER/SA-IR treatment group at each study time point will be evaluated using descriptive statistics for Part II UX001-CL201.

A GEE Model similar in construct to that performed for the 6MWT efficacy variable will be completed for the % predicted of Normal 6MWT.

In addition the cross-over treatment pathway groups may be compared with the change observed in prior treatment period for the % predicted of normal 6MWT distance. Trends in the change observed in % predicted of normal 6MWT distance will be displayed using graphical techniques.

6.7.9 Efficacy Analysis: Walking Speed Test

Gait Speed – Comfortable and Maximum Pace:

The gait speed test will be used to evaluate walking speed at a comfortable and maximum pace on a 7.62 meter (25 feet) course. The speed at which the subject can walk 7.62 meters will be measured in centimeters/second (cm/s) for the comfortable and maximum paces. Comfortable gait speed (CGS) and maximum gait speed (MGS) observed for the 12g/day SA-ER/SA-IR treatment group in Part II of UX001-CL202 will be evaluated using descriptive statistics.

A GEE analysis model will be developed to examine the change in speed (cm/s) at the comfortable pace (CGS) for the 6-month Part II analysis with study time points as categorical predictors and age, height and Baseline CGS as covariates. The same GEE model will be used to assess change in speed (cm/s) at maximum pace (MGS). The defined baselines and planned comparisons to be examined in this analysis are identified in Table 8.

In addition the cross-over treatment pathway groups may be compared with the change observed in prior treatment period for the CGS and MGS parameters. Trends in the change observed in the CGS and MGS parameters will be displayed using graphical techniques.

6.7.10 Exploratory Efficacy Analysis: Walking Speed Test

% Predicted of Normal Gait Speed – Comfortable and Maximum Pace

The gait speed of subjects relative to peers will be evaluated as a sensitivity analysis using % of height-normalized predicted speed values for CGS and MGS parameters. Predicted normal values will be calculated as described in section 6.5.2. Percent of predicted normal

CGS and MGS observed for the 12g/day SA-ER/SA-IR treatment group in Part II of UX001-CL202 at each study time point will be summarized using descriptive statistics.

GEE models similar to those performed for the CGS and MGS parameters will be completed as sensitivity analyses.

In addition the cross-over treatment pathway groups may be compared with the change observed in prior treatment period for the % predicted CGS and MGS parameters. Trends in the change observed in the % predicted CGS and MGS parameters will be displayed using graphical techniques.

6.7.11 Efficacy Analysis: Weighted Arm Lift Test

The weighted arm lift test will be used to assess the ability to raise a weighted object overhead with each arm. Performance will be measured by the number of times that a subject can lift a 1 kg dumbbell overhead in a 30-second period. The test will be performed twice, once with the left arm and once with the right arm. The number of repetitions performed on each side for the 12g/day SA-ER/SA-IR treatment group at each study time point will be evaluated using descriptive statistics on the average result of the left and right side.

A GEE analysis model will be developed to examine the change in weighted arm lift test for the 6-month Part II analysis with study time points as categorical predictors and gender, age, and baseline weighted arm lift as covariates. Baseline for these analysis will be the week 48 observation (termination visit) from UX001-CL201. The comparisons to be examined are identified in Table 8.

In addition the cross-over treatment pathway groups may be compared with the change observed in prior treatment period for weighted arm lift test. Trends in the change observed in the weighted arm lift test will be displayed using graphical techniques.

6.7.12 Efficacy Analysis: HIBM Functional Activities Scale

The HIBM-FAS will be administered to assess subject's self-reported activity limitations resulting from HIBM. Activity limitation will be measured with a total score and 3 subscale scores for mobility, upper extremity function and self-care. The individual HIBM variables are presented in Table 6. Total and subscale scores will be calculated as described in Section 6.5.2. Total and subscale scores will be evaluated for the 12g/day SA-ER/SA-IR dose at each study time point in Part II of UX001-CL202 using descriptive statistics.

A GEE analysis model will be developed to examine the change in HIBM-FAS with study time points as categorical predictors and gender, age, and baseline as covariates. Baseline for these analysis will be the week 48 observation (termination visit) from UX001-CL201. The comparisons to be examined are identified in Table 8. The GEE approach detailed above for

the analysis of the HIBM-FAS total score will be repeated for HIBM-FAS Mobility, Upper Extremity and Self-Care subscales.

In addition the cross-over treatment pathway groups may be compared with the change observed in prior treatment period for HIBM-FAS total score, as well as the individual scores for HIBM-FAS Mobility, Upper Extremity and Self-Care subscales. Trends in the change observed in the HIBM-FAS will be displayed using graphical techniques.

6.7.13 Exploratory Efficacy Analysis: Creatine Kinase

Creatine kinase (CK) samples are being assessed at baseline and the Part I termination visit, and at months 1, 3, 6, 12, 24, 36, a nd the termination visit in Part II in UX001-Cl202 for subjects who roll-over from UX001-CL201. Treatment Naïve subjects who are enrolled in Part II of this study will have a baseline assessed at the screening visit.

Changes in CK will be evaluated using descriptive and graphical summaries to evaluate change over time in CK levels after dosing with 12g/day SA-ER/SA-IR in Part II.

A GEE analysis model will be developed to examine the change in creatine kinase for the 6-month Part II analysis with study time points, dose, and baseline creatine kinase as covariates. Baseline for these analysis will be the week 48 observation (termination visit) from UX001-CL201. The comparisons to be examined are identified in Table 8.

6.8 Statistical Analysis: Effect of Changes in Muscle Strength, PROs, and Physical Function

6.8.1 Upper Extremity Muscle Strength vs. Weighted Arm Lift Test

GEE will be used to assess the relationship between changes in upper extremity muscle strength and changes in arm raising ability. Changes in HHD UE composite scores will be compared to changes in the number of repetitions performed in the weighted arm lift test. The GEE will be performed with and without treatment in the model for Part II in UX001-CL202. Additional comparisons may be made to explore the changes in these muscle strength parameters over the dosing pathways identified in Table 3 and in Table 8.

6.8.2 Lower Extremity Muscle Strength vs. 6MWT Distance

GEE will be used to assess the relationship between changes in lower extremity muscle strength and changes in the results for the 6-minute walk test (6MWT). Changes in HHD LE composite scores will be compared to changes in the 6MWT distance (as measured in meters). The GEE will be performed with and without treatment in the model for Part II in

UX001-CL202. Additional comparisons may be made to explore the changes in these muscle strength parameters over the dosing pathways identified in Table 3 and in Table 8.

6.8.3 Lower Extremity Muscle Strength vs. Gait Speed Test

GEE will be used to assess the relationship between changes in lower extremity muscle strength and changes in the results for the comfortable gait speed (CGS) and maximum gait speed (MGS) observed for the 12g/day SA-ER/SA-IR treatment group in Part II of UX001-CL202. The GEE will be performed with and without treatment in the model for Part II in UX001-CL202 to examine changes in HHD LE composite scores compared to changes in CGS and MGS (as measured in cm/s). Additional comparisons may be made to explore the changes in these muscle strength parameters over the dosing pathways identified in Table 3 and in Table 8.

6.8.4 HIBM-FAS Total and UE Subscale Score vs. HHD UE Composite Score

GEE will be used to assess the relationship between changes in self-reported functional disability and changes in upper extremity strength. Changes in HIBM-FAS total and HIBM-FAS UE subscale score will be compared to changes in HHD UE composite score. The GEE will be performed with and without treatment in the model for Part II in UX001-CL202. Additional comparisons may be made to explore the changes in these parameters over the dosing pathways identified in Table 3 and in Table 8.

6.8.5 HIBM-FAS Total and Mobility Subscale Score vs. HHD LE Composite Score

GEE will be used to assess the relationship between changes in self-reported functional disability and changes in lower extremity strength. Changes in HIBM-FAS total and HIBM-FAS Mobility subscale score will be compared to changes in HHD LE composite score. The GEE will be performed with and without treatment in the model for Part II in UX001-CL202. Additional comparisons may be made to explore the changes in these parameters over the dosing pathways identified in Table 3 and in Table 8.

6.8.6 HIBM-FAS Total and Mobility Subscale Score vs. 6MWT Distance

GEE will be used to assess the relationship between changes in self-reported functional disability and changes in walking ability (6MWT). Changes in HIBM-FAS total and HIBM-FAS Mobility subscale score will be compared to changes in 6MWT distance. The GEE will be performed with and without treatment in the model for Part II in UX001-CL202. Additional comparisons may be made to explore the changes in these parameters over the dosing pathways identified in Table 3 and in Table 8.

6.8.7 HIBM-FAS Total and Mobility Subscale Score vs. Gait Speed Test

GEE will be used to assess the relationship between changes in self-reported functional disability and changes in comfortable gait speed (CGS) and maximum gait speed (MGS). Changes in HIBM-FAS total and HIBM-FAS Mobility subscale score will be compared to changes in CGS and MGS (as measured in cm/s). The GEE will be performed with and without treatment in the model for Part II in UX001-CL202. Additional comparisons may be made to explore the changes in these parameters over the dosing pathways identified in Table 3 and in Table 8.

6.8.8 HIBM-FAS Total and UE Subscale Score vs. Weighted Arm Lift Test

GEE will be used to assess the relationship between changes in self-reported functional disability and weighted arm lift test. Changes in HIBM-FAS total and HIBM-FAS Mobility subscale score will be compared to changes in weighted arm lift test scores. The GEE will be performed with and without treatment in the model for Part II in UX001-CL202. Additional comparisons may be made to explore the changes in these parameters over the dosing pathways identified in Table 3 and in Table 8.

6.9 Statistical Analysis: Pharmacokinetics

6.9.1 Free Serum Sialic Acid (SA) Levels

Blood samples for the measurement of trough levels of free serum SA will be drawn during blood draws for clinical laboratory samples. Free serum SA samples are being assessed at baseline and the Part I termination visit, and at months 1, 3, 6, 12, 24, 36, and the termination visit in Part II in UX001-Cl202 for subjects who roll-over from UX001-CL201. Treatment Naïve subjects who are enrolled in Part II of this study will have a baseline assessed at the screening visit.

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. Free serum SA levels observed for the 12g/day SA-ER/SA-IR dose will be evaluated at each study time point using descriptive statistics.

The change in free serum SA level from Baseline to the 6-month Part II time point will be analysed using a GEE model with baseline free serum SA level as a covariate for the 12g/day SA-ER-SA-IR dose group in Part II. Comparisons identified in Table 8 will be implemented for this analysis.

6.10 Statistical Analysis: Safety

In general all safety analyses will be completed using descriptive summaries, graphs, and subject listings. No planned inferential testing of safety endpoints is planned. If after the any planned analysis it is determined by the medical writer and study medical monitor that inferential tests of significance may help to provide context for safety information these tests may be performed and identified in the CSR.

6.10.1 Adverse Events

Adverse Events will be assessed at all visits and throughout the course of the study. The number and percent of subjects with any treatment-emergent adverse events (TEAEs) will be displayed by system organ class and preferred term for each treatment group (6g/day SA-ER, 12g/day SA-ER/SA-IR). Within each preferred term, subjects will be counted only once if they had more than one event reported during the treatment period. The same summary will be performed for all serious TEAEs and all TEAEs causing discontinuation of study drug.

The number and percent of subject TEAEs will also be summarized by greatest reported severity grade (Grades 1-5) for each event preferred term by treatment group. Wherever possible, the severity of all AEs observed will be graded using the NCI CTCAE (V4.0) as follows in Table 9:

Table 9 NCI-CTCAE Common AE Grading Criteria

Grade	Description
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
4	Life-threatening consequences; urgent intervention indicated.
5	Death related to AE.
Source: Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0, Published May 28, 2009 (v4.03, June 24, 2010); USHHS/NIH/NCI * ADL=Activities for Daily Living: Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc. ** Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.	

The majority of AEs and TEAEs can be graded using the NCI-CTCAE system. Wherever possible, the severity of all AEs will be graded using the NCI CTCAE. The majority of AEs can be graded using this system. If an AE cannot be graded using the CTCAE criteria, it should be graded as mild, moderate, severe, life-threatening, or death using the definitions in Table 10.

Table 10 Mapped AE Grading Criteria

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

The number and percent of subjects reporting one or more TEAEs that map to the severity grade classification for each preferred term will be summarized by treatment group. At each level of summarization (system organ class or event preferred term) subjects are only counted once.

The number and percent of subjects experiencing Serious Adverse Events (SAE) for each preferred term will be summarized by treatment group.

The number and percent of subjects who withdraw from the study or discontinue study medication due to a TEAE or SAE will be summarized by treatment group.

The number and percent of subject TEAEs will be summarized by greatest reported relationship to study medication in as follows in Table 11.

Table 11 AE Relationship to Study Medication

Relationship	Description
Not-Related	This category applies to an AE that is clearly not related to the investigational agent/procedure, beyond a reasonable doubt. That is, another cause of the event is most plausible; and/or a clinically plausible temporal sequence is inconsistent with the onset of the event and the exposure to study drug and/or a causal relationship is considered biologically implausible.
Possibly-Related	This category applies to an AE that follows a r easonable temporal sequence from administration of the study drug and that follows a known or expected response pattern to the suspected study drug, but that could readily have been produced by a number of other factors.
Probably-Related	This category applies to an AE that is likely related to the investigational agent/procedure. T hat is, the AE has a temporal relationship to the administration of the investigational agent(s) or research intervention, follows a known or suspected pattern of response, and is strongly associated with study drug exposure.

A listing will be produced for all subjects who reported serious TEAEs or who discontinued study medication due to TEAEs.

All TEAEs will be listed individually by subject. In addition, a separate listing will be produced for AEs that are not treatment-emergent. Separate individual subject listings for SAE and TEAE leading to Study Withdrawal or discontinuation of Study Medication will also be produced.

6.10.2 Clinical Laboratory Parameters

Clinical safety laboratories (CBC, Chemistries, Creatine Kinase, Free Serum SA Levels, and Pregnancy tests) will be assessed during Part I of this study at baseline and the Part I termination visit. For subjects who roll-over from study UX001-CL201 the baseline clinical laboratory values may be derived from the last visit (week 48, or termination visit) in UX001-CL201, prior to participation in UX001-CL202.

Clinical safety laboratories (CBC, Chemistries, Creatine Kinase, and Free Serum SA Levels) will be assessed during Part II of this study at the Screening/Baseline and Months 1, 3, 6, 12, 18, 24, 30, 36, and termination visits. Pregnancy testing will be completed in Part II at the Screening/Baseline and Months 12, 24, and termination visits. For subjects who roll-over

from study UX001-CL201 and participate in Part I of this study the baseline clinical laboratory values may be derived from the last visit in Part I (Part I termination visit). For Treatment Naïve Subjects enrolled directly into Part II the baseline values will be the Screening/Baseline visit for these subjects.

Laboratory data will be monitored for safety and will be listed by subject. No descriptive information will be compiled for clinical laboratory data.

6.10.3 Vital Signs

Vital signs (Blood Pressure, respiratory rate, heart rate) will be assessed during Part I of this study at baseline and the Part I termination visit. For subjects who roll-over from study UX001-CL201 the baseline vital sign values may be derived from the last visit (week 48, or termination visit) in UX001-CL201, prior to participation in UX001-CL202.

Vital signs (Blood Pressure, respiratory rate, heart rate) will be assessed during Part II of this study at the Screening/Baseline and Months 1, 6, 12, 18, 24, 30, 36, and termination visits. For subjects who roll-over from study UX001-CL201 and participate in Part I of this study the baseline vital sign values may be derived from the last visit in Part I (Part I termination visit). For Treatment Naïve Subjects enrolled directly into Part II the baseline values will be the Screening/Baseline visit for these subjects.

Vital signs data will be monitored for safety and will be listed by subject. No descriptive information will be compiled for vital signs data.

6.10.4 Medical History

Medical History for subjects who roll-over from study UX001-CL201 will be carried forward from the UX001-CL201 study.

Medical History (and Interval History) will be assessed during Part II of this study at the Screening/Baseline and Months 1, 6, 12, 18, 24, 30, 36, and termination visits. For Treatment Naïve Subjects enrolled directly into Part II medical history (and interval history) will be assessed at the Screening/Baseline visit for these subjects.

A detailed medical history will be obtained at Screening and presented descriptively by treatment group. The medical history will solicit information on any prior or existing medical conditions that might interfere with study participation or safety. Medical History information from subjects who participate in Part I of this study and roll-over from UX001-CL201 will be carried forward from the UX001-CL201 study. For Treatment Naïve Subjects enrolled directly into Part II the medical history will be obtained at the Screening/Baseline visit for these subjects.

Medical history results for all subjects in the safety population will be reported in listing format, identifying those subjects carried over from UX001-CL201 and those Treatment Naïve Subjects enrolled into Part II.

6.10.5 Interval History

Interval History will be assessed during Part I of this study at baseline and the Part I termination visit. For subjects who roll-over from study UX001-CL201 the baseline interval history values may be derived from the last visit (week 48, or termination visit) in UX001-CL201, prior to participation in UX001-CL202.

Interval History will be assessed during Part II of this study at the Screening/Baseline and Months 1, 6, 12, 18, 24, 30, 36, and termination visits. For subjects who roll-over from study UX001-CL201 and participate in Part I of this study the baseline interval values may be derived from the last visit in Part I (Part I termination visit). For Treatment Naïve Subjects enrolled directly into Part II the baseline values will be the Screening/Baseline visit for these subjects.

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 include exacerbation or improvement in existing medical conditions (including the clinical manifestations of HIBM) that might interfere with study participation, safety, and/or positively or negatively impact performance of functional assessments. Interval history may identify under-reported AEs.

Interval history for all subjects in the safety population will be reported in listing format, identifying those subjects carried over from UX001-CL201 and those Treatment Naïve Subjects enrolled into Part II.

The number of falls experienced by subjects in Part I (6g/day SA-ER) and in Part II (12g/day SA-ER/SA-IR) treatment groups will be evaluated at each study time point using descriptive statistics.

6.10.6 Physical Examination

Physical Examinations will be assessed during Part I of this study at baseline and the Part I termination visit. For subjects who roll-over from study UX001-CL201 the baseline physical examination values may be derived from the last visit (week 48, or termination visit) in UX001-CL201, prior to participation in UX001-CL202.

Physical Examination will be assessed during Part II of this study at the Screening/Baseline and Months 1, 6, 18, 36, and termination visits. For subjects who roll-over from study UX001-CL201 and participate in Part I of this study the baseline physical examination values may be derived from the last visit in Part I (Part I termination visit). For Treatment

Naïve Subjects enrolled directly into Part II the baseline values will be the Screening/Baseline visit for these subjects.

Physical exam results for all subjects in the safety population will be reported in listing format. Changes in physical examination will be reported as adverse events.

6.10.7 Neurological Examination

Neurological Examinations will be assessed during Part I of this study at baseline and the Part I termination visit. For subjects who roll-over from study UX001-CL201 the baseline neurological examination values may be derived from the last visit (week 48, or termination visit) in UX001-CL201, prior to participation in UX001-CL202.

Neurological Examination will be assessed during Part II of this study at the Screening/Baseline and Months 6, 18, and 36 visits. For subjects who roll-over from study UX001-CL201 and participate in Part I of this study the baseline neurological examination values may be derived from the last visit in Part I (Part I termination visit). For Treatment Naïve Subjects enrolled directly into Part II the baseline values will be the Screening/Baseline visit for these subjects.

The neurological examination will include assessments of cognition, cranial nerves, motor function, coordination and gait, reflexes, and sensory function.

Neurological exam results for all subjects in the safety population will be reported in listing format. Changes in neurological examination will be reported as adverse events.

6.10.8 Pregnancy Testing

Results of pregnancy testing for females of child bearing potential will be provided in listings.

6.10.9 Other Safety Parameters

In some cases inferential statistical comparisons may be requested by the medical report writer (e.g., analysis of variance comparing vital signs or laboratory values between treatment groups). All such requests will be carried out by the statistician. P-values in such instances will serve as measures of distance to facilitate the clinical review and screening of these numerous variables.

7 REFERENCES

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Wallenstein S. and Wittes J. The Power of the Mantel-Haenszel Test. Biometrics 1993;49 (4):1077–1087.

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8 APPENDICES

8.1 List of Prospective Tables and Figures

The following is a list of the planned Tables and Figures prospectively identified for the planned analyses described in this SAP. A separate document will be completed for programming specifications that provides details on the unique mock Tables, Figures, and Listings. The mock shells may be updated throughout the course of programming and review without amendment of this SAP.

Included is a list of the planned tables for this Study. Corresponding figures will be developed for those efficacy endpoints to display trends, frequencies, and modeled output were appropriate to better facilitate the understanding of the data and results. Note that additional tables and figures, not listed herein, may be generated to better understand study results. These additional tables and figures will be identified in the final publication of study results. The SAP will not be amended to identify additional analyses.

The final numbering and presentation order of the tables and figures completed to support the analyses conducted for UX001-CL202 will be determined prior to final delivery of the analyses. In general, clinical efficacy tables and figures will be grouped first by analysis type (as identified in Table 8), and then by endpoint.

Table ID[1]	Table Description[2]
1	Subject Disposition
2	Demographics and Baseline Characteristics- Safety Population
3	Demographics and Baseline Characteristics- ITT Population
4	Number of Doses Administered- Safety Population
5	Number of Doses Administered- ITT Population
6	Prior Medication
7	Concomitant Medication
8	Interval History- Number of Falls
9	TEAE- Overall Summary

Table ID[(1)]	Table Description[(2)]
10	TEAE- by SOC and PT (including second table of TEAE by descending frequency of PT)
11	Serious TEAE- by SOC and PT
12	TEAE Causing Discontinuation- by SOC and PT
13	TEAE by Severity- by SOC and PT
14	TEAE by Relationship- by SOC and PT
15	Elbow Extension (kg)- Summary
16	Elbow Extension (kg)- Primary Analysis #1
17	Elbow Extension (kg)- Primary Analysis #1- 6MWT >= 200
18	Elbow Extension (kg)- Primary Analysis #2
19	Elbow Extension (kg)- Primary Analysis #2- 6MWT >= 200
20	Elbow Extension (kg)- Primary Analysis #3
21	Elbow Extension (kg)- Primary Analysis #3- 6MWT >= 200
22	Elbow Extension (kg)- Secondary Analysis
23	Elbow Extension (kg)- Secondary Analysis- 6MWT >= 200
24	Elbow Extension (kg)- Treatment Naïve Primary Analysis
25	Elbow Extension (kg)- Treatment Naïve Secondary Analysis
26	Elbow Extension (kg)- Treatment Naïve Secondary Analysis- 6MWT >= 200
27	Elbow Flexion (kg)- Summary
28	Elbow Flexion (kg)- Primary Analysis #1
29	Elbow Flexion (kg)- Primary Analysis #1- 6MWT >= 200
30	Elbow Flexion (kg)- Primary Analysis #2
31	Elbow Flexion (kg)- Primary Analysis #2- 6MWT >= 200

Table ID[(1)]	Table Description[(2)]
32	Elbow Flexion (kg)- Primary Analysis #3
33	Elbow Flexion (kg)- Primary Analysis #3- 6MWT >= 200
34	Elbow Flexion (kg)- Secondary Analysis
35	Elbow Flexion (kg)- Secondary Analysis- 6MWT >= 200
36	Elbow Flexion (kg)- Treatment Naïve Primary Analysis
37	Elbow Flexion (kg)- Treatment Naïve Secondary Analysis
38	Elbow Flexion (kg)- Treatment Naïve Secondary Analysis- 6MWT >= 200
39	Grip (kg)- Summary
40	Grip (kg)- Primary Analysis #1
41	Grip (kg)- Primary Analysis #1- 6MWT >= 200
42	Grip (kg)- Primary Analysis #2
43	Grip (kg)- Primary Analysis #2- 6MWT >= 200
44	Grip (kg)- Primary Analysis #3
45	Grip (kg)- Primary Analysis #3- 6MWT >= 200
46	Grip (kg)- Secondary Analysis
47	Grip (kg)- Secondary Analysis- 6MWT >= 200
48	Grip (kg)- Treatment Naïve Primary Analysis
49	Grip (kg)- Treatment Naïve Secondary Analysis
50	Grip (kg)- Treatment Naïve Secondary Analysis- 6MWT >= 200
51	Hip Abduction (kg)- Summary
52	Hip Abduction (kg)- Primary Analysis #1
53	Hip Abduction (kg)- Primary Analysis #1- 6MWT >= 200

Table ID[(1)]	Table Description[(2)]
54	Hip Abduction (kg)- Primary Analysis #2
55	Hip Abduction (kg)- Primary Analysis #2- 6MWT >= 200
56	Hip Abduction (kg)- Primary Analysis #3
57	Hip Abduction (kg)- Primary Analysis #3- 6MWT >= 200
58	Hip Abduction (kg)- Secondary Analysis
59	Hip Abduction (kg)- Secondary Analysis- 6MWT >= 200
60	Hip Abduction (kg)- Treatment Naïve Primary Analysis
61	Hip Abduction (kg)- Treatment Naïve Secondary Analysis
62	Hip Abduction (kg)- Treatment Naïve Secondary Analysis- 6MWT >= 200
63	Hip Adduction (kg)- Summary
64	Hip Adduction (kg)- Primary Analysis #1
65	Hip Adduction (kg)- Primary Analysis #1- 6MWT >= 200
66	Hip Adduction (kg)- Primary Analysis #2
67	Hip Adduction (kg)- Primary Analysis #2- 6MWT >= 200
68	Hip Adduction (kg)- Primary Analysis #3
69	Hip Adduction (kg)- Primary Analysis #3- 6MWT >= 200
70	Hip Adduction (kg)- Secondary Analysis
71	Hip Adduction (kg)- Secondary Analysis- 6MWT >= 200
72	Hip Adduction (kg)- Treatment Naïve Primary Analysis
73	Hip Adduction (kg)- Treatment Naïve Secondary Analysis
74	Hip Adduction (kg)- Treatment Naïve Secondary Analysis- 6MWT >= 200
75	Hip Extension (kg)- Summary

Table ID[(1)]	Table Description[(2)]
76	Hip Extension (kg)- Primary Analysis #1
77	Hip Extension (kg)- Primary Analysis #1- 6MWT >= 200
78	Hip Extension (kg)- Primary Analysis #2
79	Hip Extension (kg)- Primary Analysis #2- 6MWT >= 200
80	Hip Extension (kg)- Primary Analysis #3
81	Hip Extension (kg)- Primary Analysis #3- 6MWT >= 200
82	Hip Extension (kg)- Secondary Analysis
83	Hip Extension (kg)- Secondary Analysis- 6MWT >= 200
84	Hip Extension (kg)- Treatment Naïve Primary Analysis
85	Hip Extension (kg)- Treatment Naïve Secondary Analysis
86	Hip Extension (kg)- Treatment Naïve Secondary Analysis- 6MWT >= 200
87	Hip Flexion (kg)- Summary
88	Hip Flexion (kg)- Primary Analysis #1
89	Hip Flexion (kg)- Primary Analysis #1- 6MWT >= 200
90	Hip Flexion (kg)- Primary Analysis #2
91	Hip Flexion (kg)- Primary Analysis #2- 6MWT >= 200
92	Hip Flexion (kg)- Primary Analysis #3
93	Hip Flexion (kg)- Primary Analysis #3- 6MWT >= 200
94	Hip Flexion (kg)- Secondary Analysis
95	Hip Flexion (kg)- Secondary Analysis- 6MWT >= 200
96	Hip Flexion (kg)- Treatment Naïve Primary Analysis
97	Hip Flexion (kg)- Treatment Naïve Secondary Analysis

Table ID[1]	Table Description[2]
98	Hip Flexion (kg)- Treatment Naïve Secondary Analysis- 6MWT >= 200
99	Key (kg)- Summary
100	Key (kg)- Primary Analysis #1
101	Key (kg)- Primary Analysis #1- 6MWT >= 200
102	Key (kg)- Primary Analysis #2
103	Key (kg)- Primary Analysis #2- 6MWT >= 200
104	Key (kg)- Primary Analysis #3
105	Key (kg)- Primary Analysis #3- 6MWT >= 200
106	Key (kg)- Secondary Analysis
107	Key (kg)- Secondary Analysis- 6MWT >= 200
108	Key (kg)- Treatment Naïve Primary Analysis
109	Key (kg)- Treatment Naïve Secondary Analysis
110	Key (kg)- Treatment Naïve Secondary Analysis- 6MWT >= 200
111	Knee Extension (kg)- Summary
112	Knee Extension (kg)- Primary Analysis #1
113	Knee Extension (kg)- Primary Analysis #1- 6MWT >= 200
114	Knee Extension (kg)- Primary Analysis #2
115	Knee Extension (kg)- Primary Analysis #2- 6MWT >= 200
116	Knee Extension (kg)- Primary Analysis #3
117	Knee Extension (kg)- Primary Analysis #3- 6MWT >= 200
118	Knee Extension (kg)- Secondary Analysis
119	Knee Extension (kg)- Secondary Analysis- 6MWT >= 200

Table ID[(1)]	Table Description[(2)]
120	Knee Extension (kg)- Treatment Naïve Primary Analysis
121	Knee Extension (kg)- Treatment Naïve Secondary Analysis
122	Knee Extension (kg)- Treatment Naïve Secondary Analysis- 6MWT >= 200
123	Knee Flexion (kg)- Summary
124	Knee Flexion (kg)- Primary Analysis #1
125	Knee Flexion (kg)- Primary Analysis #1- 6MWT >= 200
126	Knee Flexion (kg)- Primary Analysis #2
127	Knee Flexion (kg)- Primary Analysis #2- 6MWT >= 200
128	Knee Flexion (kg)- Primary Analysis #3
129	Knee Flexion (kg)- Primary Analysis #3- 6MWT >= 200
130	Knee Flexion (kg)- Secondary Analysis
131	Knee Flexion (kg)- Secondary Analysis- 6MWT >= 200
132	Knee Flexion (kg)- Treatment Naïve Primary Analysis
133	Knee Flexion (kg)- Treatment Naïve Secondary Analysis
134	Knee Flexion (kg)- Treatment Naïve Secondary Analysis- 6MWT >= 200
135	Palmar (kg)- Summary
136	Palmar (kg)- Primary Analysis #1
137	Palmar (kg)- Primary Analysis #1- 6MWT >= 200
138	Palmar (kg)- Primary Analysis #2
139	Palmar (kg)- Primary Analysis #2- 6MWT >= 200
140	Palmar (kg)- Primary Analysis #3
141	Palmar (kg)- Primary Analysis #3- 6MWT >= 200

Table ID[(1)]	Table Description[(2)]
142	Palmar (kg)- Secondary Analysis
143	Palmar (kg)- Secondary Analysis- 6MWT >= 200
144	Palmar (kg)- Treatment Naïve Primary Analysis
145	Palmar (kg)- Treatment Naïve Secondary Analysis
146	Palmar (kg)- Treatment Naïve Secondary Analysis- 6MWT >= 200
147	Shoulder Abduction (kg)- Summary
148	Shoulder Abduction (kg)- Primary Analysis #1
149	Shoulder Abduction (kg)- Primary Analysis #1- 6MWT >= 200
150	Shoulder Abduction (kg)- Primary Analysis #2
151	Shoulder Abduction (kg)- Primary Analysis #2- 6MWT >= 200
152	Shoulder Abduction (kg)- Primary Analysis #3
153	Shoulder Abduction (kg)- Primary Analysis #3- 6MWT >= 200
154	Shoulder Abduction (kg)- Secondary Analysis
155	Shoulder Abduction (kg)- Secondary Analysis- 6MWT >= 200
156	Shoulder Abduction (kg)- Treatment Naïve Primary Analysis
157	Shoulder Abduction (kg)- Treatment Naïve Secondary Analysis
158	Shoulder Abduction (kg)- Treatment Naïve Secondary Analysis- 6MWT >= 200
159	Tip (kg)- Summary
160	Tip (kg)- Primary Analysis #1
161	Tip (kg)- Primary Analysis #1- 6MWT >= 200
162	Tip (kg)- Primary Analysis #2
163	Tip (kg)- Primary Analysis #2- 6MWT >= 200

Table ID[(1)]	Table Description[(2)]
164	Tip (kg)- Primary Analysis #3
165	Tip (kg)- Primary Analysis #3- 6MWT >= 200
166	Tip (kg)- Secondary Analysis
167	Tip (kg)- Secondary Analysis- 6MWT >= 200
168	Tip (kg)- Treatment Naïve Primary Analysis
169	Tip (kg)- Treatment Naïve Secondary Analysis
170	Tip (kg)- Treatment Naïve Secondary Analysis- 6MWT >= 200
171	HHD Upper Extremity CS- Summary
172	HHD Upper Extremity CS- Primary Analysis #1
173	HHD Upper Extremity CS- Primary Analysis #1- 6MWT >= 200
174	HHD Upper Extremity CS- Primary Analysis #2
175	HHD Upper Extremity CS- Primary Analysis #2- 6MWT >= 200
176	HHD Upper Extremity CS- Primary Analysis #3
177	HHD Upper Extremity CS- Primary Analysis #3- 6MWT >= 200
178	HHD Upper Extremity CS- Secondary Analysis
179	HHD Upper Extremity CS- Secondary Analysis- 6MWT >= 200
180	HHD Upper Extremity CS- Treatment Naïve Primary Analysis
181	HHD Upper Extremity CS- Treatment Naïve Secondary Analysis
182	HHD Upper Extremity CS- Treatment Naïve Secondary Analysis- 6MWT >= 200
183	HHD Lower Extremity CS- Summary
184	HHD Lower Extremity CS- Primary Analysis #1
185	HHD Lower Extremity CS- Primary Analysis #1- 6MWT >= 200

Table ID[(1)]	Table Description[(2)]
186	HHD Lower Extremity CS- Primary Analysis #2
187	HHD Lower Extremity CS- Primary Analysis #2- 6MWT >= 200
188	HHD Lower Extremity CS- Primary Analysis #3
189	HHD Lower Extremity CS- Primary Analysis #3- 6MWT >= 200
190	HHD Lower Extremity CS- Secondary Analysis
191	HHD Lower Extremity CS- Secondary Analysis- 6MWT >= 200
192	HHD Lower Extremity CS- Treatment Naïve Primary Analysis
193	HHD Lower Extremity CS- Treatment Naïve Secondary Analysis
194	HHD Lower Extremity CS- Treatment Naïve Secondary Analysis- 6MWT >= 200
195	6MWT- Summary
196	6MWT- Primary Analysis #1
197	6MWT- Primary Analysis #1- 6MWT >= 200
198	6MWT- Primary Analysis #2
199	6MWT- Primary Analysis #2- 6MWT >= 200
200	6MWT- Primary Analysis #3
201	6MWT- Primary Analysis #3- 6MWT >= 200
202	6MWT- Secondary Analysis
203	6MWT- Secondary Analysis- 6MWT >= 200
204	6MWT- Treatment Naïve Primary Analysis
205	6MWT- Treatment Naïve Secondary Analysis
206	6MWT- Treatment Naïve Secondary Analysis- 6MWT >= 200
207	Comfortable Gait Speed- Summary

Table ID[(1)]	Table Description[(2)]
208	Comfortable Gait Speed- Primary Analysis #1
209	Comfortable Gait Speed- Primary Analysis #1- 6MWT >= 200
210	Comfortable Gait Speed- Primary Analysis #2
211	Comfortable Gait Speed- Primary Analysis #2- 6MWT >= 200
212	Comfortable Gait Speed- Primary Analysis #3
213	Comfortable Gait Speed- Primary Analysis #3- 6MWT >= 200
214	Comfortable Gait Speed- Secondary Analysis
215	Comfortable Gait Speed- Secondary Analysis- 6MWT >= 200
216	Comfortable Gait Speed- Treatment Naïve Primary Analysis
217	Comfortable Gait Speed- Treatment Naïve Secondary Analysis
218	Comfortable Gait Speed- Treatment Naïve Secondary Analysis- 6MWT >= 200
219	Maximum Gait Speed- Summary
220	Maximum Gait Speed- Primary Analysis #1
221	Maximum Gait Speed- Primary Analysis #1- 6MWT >= 200
222	Maximum Gait Speed- Primary Analysis #2
223	Maximum Gait Speed- Primary Analysis #2- 6MWT >= 200
224	Maximum Gait Speed- Primary Analysis #3
225	Maximum Gait Speed- Primary Analysis #3- 6MWT >= 200
226	Maximum Gait Speed- Secondary Analysis
227	Maximum Gait Speed- Secondary Analysis- 6MWT >= 200
228	Maximum Gait Speed- Treatment Naïve Primary Analysis
229	Maximum Gait Speed- Treatment Naïve Secondary Analysis

Table ID[(1)]	Table Description[(2)]
230	Maximum Gait Speed- Treatment Naïve Secondary Analysis- 6MWT >= 200
231	Weighted Arm Lift- Summary
232	Weighted Arm Lift- Primary Analysis #1
233	Weighted Arm Lift- Primary Analysis #1- 6MWT >= 200
234	Weighted Arm Lift- Primary Analysis #2
235	Weighted Arm Lift- Primary Analysis #2- 6MWT >= 200
236	Weighted Arm Lift- Primary Analysis #3
237	Weighted Arm Lift- Primary Analysis #3- 6MWT >= 200
238	Weighted Arm Lift- Secondary Analysis
239	Weighted Arm Lift- Secondary Analysis- 6MWT >= 200
240	Weighted Arm Lift- Treatment Naïve Primary Analysis
241	Weighted Arm Lift- Treatment Naïve Secondary Analysis
242	Weighted Arm Lift- Treatment Naïve Secondary Analysis- 6MWT >= 200
243	Elbow Extension (kg)- % Predicted- Summary
244	Elbow Extension (kg)- % Predicted- Primary Analysis #1
245	Elbow Extension (kg)- % Predicted- Primary Analysis #1- 6MWT >= 200
246	Elbow Extension (kg)- % Predicted- Primary Analysis #2
247	Elbow Extension (kg)- % Predicted- Primary Analysis #2- 6MWT >= 200
248	Elbow Extension (kg)- % Predicted- Primary Analysis #3
249	Elbow Extension (kg)- % Predicted- Primary Analysis #3- 6MWT >= 200
250	Elbow Extension (kg)- % Predicted- Secondary Analysis
251	Elbow Extension (kg)- % Predicted- Secondary Analysis- 6MWT >= 200

Table ID[(1)]	Table Description[(2)]
252	Elbow Extension (kg)- % Predicted- Treatment Naïve Primary Analysis
253	Elbow Extension (kg)- % Predicted- Treatment Naïve Secondary Analysis
254	Elbow Extension (kg)- % Predicted- Treatment Naïve Secondary Analysis- 6MWT >= 200
255	Elbow Flexion (kg)- % Predicted- Summary
256	Elbow Flexion (kg)- % Predicted- Primary Analysis #1
257	Elbow Flexion (kg)- % Predicted- Primary Analysis #1- 6MWT >= 200
258	Elbow Flexion (kg)- % Predicted- Primary Analysis #2
259	Elbow Flexion (kg)- % Predicted- Primary Analysis #2- 6MWT >= 200
260	Elbow Flexion (kg)- % Predicted- Primary Analysis #3
261	Elbow Flexion (kg)- % Predicted- Primary Analysis #3- 6MWT >= 200
262	Elbow Flexion (kg)- % Predicted- Secondary Analysis
263	Elbow Flexion (kg)- % Predicted- Secondary Analysis- 6MWT >= 200
264	Elbow Flexion (kg)- % Predicted- Treatment Naïve Primary Analysis
265	Elbow Flexion (kg)- % Predicted- Treatment Naïve Secondary Analysis
266	Elbow Flexion (kg)- % Predicted- Treatment Naïve Secondary Analysis- 6MWT >= 200
267	Grip (kg)- % Predicted- Summary
268	Grip (kg)- % Predicted- Primary Analysis #1
269	Grip (kg)- % Predicted- Primary Analysis #1- 6MWT >= 200
270	Grip (kg)- % Predicted- Primary Analysis #2
271	Grip (kg)- % Predicted- Primary Analysis #2- 6MWT >= 200
272	Grip (kg)- % Predicted- Primary Analysis #3
273	Grip (kg)- % Predicted- Primary Analysis #3- 6MWT >= 200

Table ID[(1)]	Table Description[(2)]
274	Grip (kg)- % Predicted- Secondary Analysis
275	Grip (kg)- % Predicted- Secondary Analysis- 6MWT >= 200
276	Grip (kg)- % Predicted- Treatment Naïve Primary Analysis
277	Grip (kg)- % Predicted- Treatment Naïve Secondary Analysis
278	Grip (kg)- % Predicted- Treatment Naïve Secondary Analysis- 6MWT >= 200
279	Hip Abduction (kg)- % Predicted- Summary
280	Hip Abduction (kg)- % Predicted- Primary Analysis #1
281	Hip Abduction (kg)- % Predicted- Primary Analysis #1- 6MWT >= 200
282	Hip Abduction (kg)- % Predicted- Primary Analysis #2
283	Hip Abduction (kg)- % Predicted- Primary Analysis #2- 6MWT >= 200
284	Hip Abduction (kg)- % Predicted- Primary Analysis #3
285	Hip Abduction (kg)- % Predicted- Primary Analysis #3- 6MWT >= 200
286	Hip Abduction (kg)- % Predicted- Secondary Analysis
287	Hip Abduction (kg)- % Predicted- Secondary Analysis- 6MWT >= 200
288	Hip Abduction (kg)- % Predicted- Treatment Naïve Primary Analysis
289	Hip Abduction (kg)- % Predicted- Treatment Naïve Secondary Analysis
290	Hip Abduction (kg)- % Predicted- Treatment Naïve Secondary Analysis- 6MWT >= 200
291	Hip Adduction (kg)- % Predicted- Summary
292	Hip Adduction (kg)- % Predicted- Primary Analysis #1
293	Hip Adduction (kg)- % Predicted- Primary Analysis #1- 6MWT >= 200
294	Hip Adduction (kg)- % Predicted- Primary Analysis #2
295	Hip Adduction (kg)- % Predicted- Primary Analysis #2- 6MWT >= 200

Table ID[1]	Table Description[2]
296	Hip Adduction (kg)- % Predicted- Primary Analysis #3
297	Hip Adduction (kg)- % Predicted- Primary Analysis #3- 6MWT >= 200
298	Hip Adduction (kg)- % Predicted- Secondary Analysis
299	Hip Adduction (kg)- % Predicted- Secondary Analysis- 6MWT >= 200
300	Hip Adduction (kg)- % Predicted- Treatment Naïve Primary Analysis
301	Hip Adduction (kg)- % Predicted- Treatment Naïve Secondary Analysis
302	Hip Adduction (kg)- % Predicted- Treatment Naïve Secondary Analysis- 6MWT >= 200
303	Hip Extension (kg)- % Predicted- Summary
304	Hip Extension (kg)- % Predicted- Primary Analysis #1
305	Hip Extension (kg)- % Predicted- Primary Analysis #1- 6MWT >= 200
306	Hip Extension (kg)- % Predicted- Primary Analysis #2
307	Hip Extension (kg)- % Predicted- Primary Analysis #2- 6MWT >= 200
308	Hip Extension (kg)- % Predicted- Primary Analysis #3
309	Hip Extension (kg)- % Predicted- Primary Analysis #3- 6MWT >= 200
310	Hip Extension (kg)- % Predicted- Secondary Analysis
311	Hip Extension (kg)- % Predicted- Secondary Analysis- 6MWT >= 200
312	Hip Extension (kg)- % Predicted- Treatment Naïve Primary Analysis
313	Hip Extension (kg)- % Predicted- Treatment Naïve Secondary Analysis
314	Hip Extension (kg)- % Predicted- Treatment Naïve Secondary Analysis- 6MWT >= 200
315	Hip Flexion (kg)- % Predicted- Summary
316	Hip Flexion (kg)- % Predicted- Primary Analysis #1
317	Hip Flexion (kg)- % Predicted- Primary Analysis #1- 6MWT >= 200

Table ID[1]	Table Description[2]
318	Hip Flexion (kg)- % Predicted- Primary Analysis #2
319	Hip Flexion (kg)- % Predicted- Primary Analysis #2- 6MWT >= 200
320	Hip Flexion (kg)- % Predicted- Primary Analysis #3
321	Hip Flexion (kg)- % Predicted- Primary Analysis #3- 6MWT >= 200
322	Hip Flexion (kg)- % Predicted- Secondary Analysis
323	Hip Flexion (kg)- % Predicted- Secondary Analysis- 6MWT >= 200
324	Hip Flexion (kg)- % Predicted- Treatment Naïve Primary Analysis
325	Hip Flexion (kg)- % Predicted- Treatment Naïve Secondary Analysis
326	Hip Flexion (kg)- % Predicted- Treatment Naïve Secondary Analysis- 6MWT >= 200
327	Key (kg)- % Predicted- Summary
328	Key (kg)- % Predicted- Primary Analysis #1
329	Key (kg)- % Predicted- Primary Analysis #1- 6MWT >= 200
330	Key (kg)- % Predicted- Primary Analysis #2
331	Key (kg)- % Predicted- Primary Analysis #2- 6MWT >= 200
332	Key (kg)- % Predicted- Primary Analysis #3
333	Key (kg)- % Predicted- Primary Analysis #3- 6MWT >= 200
334	Key (kg)- % Predicted- Secondary Analysis
335	Key (kg)- % Predicted- Secondary Analysis- 6MWT >= 200
336	Key (kg)- % Predicted- Treatment Naïve Primary Analysis
337	Key (kg)- % Predicted- Treatment Naïve Secondary Analysis
338	Key (kg)- % Predicted- Treatment Naïve Secondary Analysis- 6MWT >= 200
339	Knee Extension (kg)- % Predicted- Summary

Table ID[(1)]	Table Description[(2)]
340	Knee Extension (kg)- % Predicted- Primary Analysis #1
341	Knee Extension (kg)- % Predicted- Primary Analysis #1- 6MWT >= 200
342	Knee Extension (kg)- % Predicted- Primary Analysis #2
343	Knee Extension (kg)- % Predicted- Primary Analysis #2- 6MWT >= 200
344	Knee Extension (kg)- % Predicted- Primary Analysis #3
345	Knee Extension (kg)- % Predicted- Primary Analysis #3- 6MWT >= 200
346	Knee Extension (kg)- % Predicted- Secondary Analysis
347	Knee Extension (kg)- % Predicted- Secondary Analysis- 6MWT >= 200
348	Knee Extension (kg)- % Predicted- Treatment Naïve Primary Analysis
349	Knee Extension (kg)- % Predicted- Treatment Naïve Secondary Analysis
350	Knee Extension (kg)- % Predicted- Treatment Naïve Secondary Analysis- 6MWT >= 200
351	Knee Flexion (kg)- % Predicted- Summary
352	Knee Flexion (kg)- % Predicted- Primary Analysis #1
353	Knee Flexion (kg)- % Predicted- Primary Analysis #1- 6MWT >= 200
354	Knee Flexion (kg)- % Predicted- Primary Analysis #2
355	Knee Flexion (kg)- % Predicted- Primary Analysis #2- 6MWT >= 200
356	Knee Flexion (kg)- % Predicted- Primary Analysis #3
357	Knee Flexion (kg)- % Predicted- Primary Analysis #3- 6MWT >= 200
358	Knee Flexion (kg)- % Predicted- Secondary Analysis
359	Knee Flexion (kg)- % Predicted- Secondary Analysis- 6MWT >= 200
360	Knee Flexion (kg)- % Predicted- Treatment Naïve Primary Analysis
361	Knee Flexion (kg)- % Predicted- Treatment Naïve Secondary Analysis

Table ID[1]	Table Description[2]
362	Knee Flexion (kg)- % Predicted- Treatment Naïve Secondary Analysis- 6MWT >= 200
363	Palmar (kg)- % Predicted- Summary
364	Palmar (kg)- % Predicted- Primary Analysis #1
365	Palmar (kg)- % Predicted- Primary Analysis #1- 6MWT >= 200
366	Palmar (kg)- % Predicted- Primary Analysis #2
367	Palmar (kg)- % Predicted- Primary Analysis #2- 6MWT >= 200
368	Palmar (kg)- % Predicted- Primary Analysis #3
369	Palmar (kg)- % Predicted- Primary Analysis #3- 6MWT >= 200
370	Palmar (kg)- % Predicted- Secondary Analysis
371	Palmar (kg)- % Predicted- Secondary Analysis- 6MWT >= 200
372	Palmar (kg)- % Predicted- Treatment Naïve Primary Analysis
373	Palmar (kg)- % Predicted- Treatment Naïve Secondary Analysis
374	Palmar (kg)- % Predicted- Treatment Naïve Secondary Analysis- 6MWT >= 200
375	Shoulder Abduction (kg)- % Predicted- Summary
376	Shoulder Abduction (kg)- % Predicted- Primary Analysis #1
377	Shoulder Abduction (kg)- % Predicted- Primary Analysis #1- 6MWT >= 200
378	Shoulder Abduction (kg)- % Predicted- Primary Analysis #2
379	Shoulder Abduction (kg)- % Predicted- Primary Analysis #2- 6MWT >= 200
380	Shoulder Abduction (kg)- % Predicted- Primary Analysis #3
381	Shoulder Abduction (kg)- % Predicted- Primary Analysis #3- 6MWT >= 200
382	Shoulder Abduction (kg)- % Predicted- Secondary Analysis
383	Shoulder Abduction (kg)- % Predicted- Secondary Analysis- 6MWT >= 200

Table ID[(1)]	Table Description[(2)]
384	Shoulder Abduction (kg)- % Predicted- Treatment Naïve Primary Analysis
385	Shoulder Abduction (kg)- % Predicted- Treatment Naïve Secondary Analysis
386	Shoulder Abduction (kg)- % Predicted- Treatment Naïve Secondary Analysis- 6MWT >= 200
387	Tip (kg)- % Predicted- Summary
388	Tip (kg)- % Predicted- Primary Analysis #1
389	Tip (kg)- % Predicted- Primary Analysis #1- 6MWT >= 200
390	Tip (kg)- % Predicted- Primary Analysis #2
391	Tip (kg)- % Predicted- Primary Analysis #2- 6MWT >= 200
392	Tip (kg)- % Predicted- Primary Analysis #3
393	Tip (kg)- % Predicted- Primary Analysis #3- 6MWT >= 200
394	Tip (kg)- % Predicted- Secondary Analysis
395	Tip (kg)- % Predicted- Secondary Analysis- 6MWT >= 200
396	Tip (kg)- % Predicted- Treatment Naïve Primary Analysis
397	Tip (kg)- % Predicted- Treatment Naïve Secondary Analysis
398	Tip (kg)- % Predicted- Treatment Naïve Secondary Analysis- 6MWT >= 200
399	6MWT- % Predicted- Summary
400	6MWT- % Predicted- Primary Analysis #1
401	6MWT- % Predicted- Primary Analysis #1- 6MWT >= 200
402	6MWT- % Predicted- Primary Analysis #2
403	6MWT- % Predicted- Primary Analysis #2- 6MWT >= 200
404	6MWT- % Predicted- Primary Analysis #3
405	6MWT- % Predicted- Primary Analysis #3- 6MWT >= 200

Table ID[(1)]	Table Description[(2)]
406	6MWT- % Predicted- Secondary Analysis
407	6MWT- % Predicted- Secondary Analysis- 6MWT >= 200
408	6MWT- % Predicted- Treatment Naïve Primary Analysis
409	6MWT- % Predicted- Treatment Naïve Secondary Analysis
410	6MWT- % Predicted- Treatment Naïve Secondary Analysis- 6MWT >= 200
411	Comfortable Gait Speed- % Predicted- Summary
412	Comfortable Gait Speed- % Predicted- Primary Analysis #1
413	Comfortable Gait Speed- % Predicted- Primary Analysis #1- 6MWT >= 200
414	Comfortable Gait Speed- % Predicted- Primary Analysis #2
415	Comfortable Gait Speed- % Predicted- Primary Analysis #2- 6MWT >= 200
416	Comfortable Gait Speed- % Predicted- Primary Analysis #3
417	Comfortable Gait Speed- % Predicted- Primary Analysis #3- 6MWT >= 200
418	Comfortable Gait Speed- % Predicted- Secondary Analysis
419	Comfortable Gait Speed- % Predicted- Secondary Analysis- 6MWT >= 200
420	Comfortable Gait Speed- % Predicted- Treatment Naïve Primary Analysis
421	Comfortable Gait Speed- % Predicted- Treatment Naïve Secondary Analysis
422	Comfortable Gait Speed- % Predicted- Treatment Naïve Secondary Analysis- 6MWT >= 200
423	Maximum Gait Speed- % Predicted- Summary
424	Maximum Gait Speed- % Predicted- Primary Analysis #1
425	Maximum Gait Speed- % Predicted- Primary Analysis #1- 6MWT >= 200
426	Maximum Gait Speed- % Predicted- Primary Analysis #2
427	Maximum Gait Speed- % Predicted- Primary Analysis #2- 6MWT >= 200

Table ID[(1)]	Table Description[(2)]
428	Maximum Gait Speed- % Predicted- Primary Analysis #3
429	Maximum Gait Speed- % Predicted- Primary Analysis #3- 6MWT >= 200
430	Maximum Gait Speed- % Predicted- Secondary Analysis
431	Maximum Gait Speed- % Predicted- Secondary Analysis- 6MWT >= 200
432	Maximum Gait Speed- % Predicted- Treatment Naïve Primary Analysis
433	Maximum Gait Speed- % Predicted- Treatment Naïve Secondary Analysis
434	Maximum Gait Speed- % Predicted- Treatment Naïve Secondary Analysis- 6MWT >= 200
435	FAS Total Score- Summary
436	FAS Total Score- Primary Analysis #1
437	FAS Total Score- Primary Analysis #1- 6MWT >= 200
438	FAS Total Score- Primary Analysis #2
439	FAS Total Score- Primary Analysis #2- 6MWT >= 200
440	FAS Total Score- Primary Analysis #3
441	FAS Total Score- Primary Analysis #3- 6MWT >= 200
442	FAS Total Score- Secondary Analysis
443	FAS Total Score- Secondary Analysis- 6MWT >= 200
444	FAS Total Score- Treatment Naïve Primary Analysis
445	FAS Total Score- Treatment Naïve Secondary Analysis
446	FAS Total Score- Treatment Naïve Secondary Analysis- 6MWT >= 200
447	FAS Mobility Score- Summary
448	FAS Mobility Score- Primary Analysis #1
449	FAS Mobility Score- Primary Analysis #1- 6MWT >= 200

Table ID[(1)]	Table Description[(2)]
450	FAS Mobility Score- Primary Analysis #2
451	FAS Mobility Score- Primary Analysis #2- 6MWT >= 200
452	FAS Mobility Score- Primary Analysis #3
453	FAS Mobility Score- Primary Analysis #3- 6MWT >= 200
454	FAS Mobility Score- Secondary Analysis
455	FAS Mobility Score- Secondary Analysis- 6MWT >= 200
456	FAS Mobility Score- Treatment Naïve Primary Analysis
457	FAS Mobility Score- Treatment Naïve Secondary Analysis
458	FAS Mobility Score- Treatment Naïve Secondary Analysis- 6MWT >= 200
459	FAS Upper Extremity Score- Summary
460	FAS Upper Extremity Score- Primary Analysis #1
461	FAS Upper Extremity Score- Primary Analysis #1- 6MWT >= 200
462	FAS Upper Extremity Score- Primary Analysis #2
463	FAS Upper Extremity Score- Primary Analysis #2- 6MWT >= 200
464	FAS Upper Extremity Score- Primary Analysis #3
465	FAS Upper Extremity Score- Primary Analysis #3- 6MWT >= 200
466	FAS Upper Extremity Score- Secondary Analysis
467	FAS Upper Extremity Score- Secondary Analysis- 6MWT >= 200
468	FAS Upper Extremity Score- Treatment Naïve Primary Analysis
469	FAS Upper Extremity Score- Treatment Naïve Secondary Analysis
470	FAS Upper Extremity Score- Treatment Naïve Secondary Analysis- 6MWT >= 200
471	FAS Self-care Score- Summary

Table ID[(1)]	Table Description[(2)]
472	FAS Self-care Score- Primary Analysis #1
473	FAS Self-care Score- Primary Analysis #1- 6MWT >= 200
474	FAS Self-care Score- Primary Analysis #2
475	FAS Self-care Score- Primary Analysis #2- 6MWT >= 200
476	FAS Self-care Score- Primary Analysis #3
477	FAS Self-care Score- Primary Analysis #3- 6MWT >= 200
478	FAS Self-care Score- Secondary Analysis
479	FAS Self-care Score- Secondary Analysis- 6MWT >= 200
480	FAS Self-care Score- Treatment Naïve Primary Analysis
481	FAS Self-care Score- Treatment Naïve Secondary Analysis
482	FAS Self-care Score- Treatment Naïve Secondary Analysis- 6MWT >= 200
483	Free Serum SA- Summary
484	Free Serum SA- Primary Analysis #1
485	Free Serum SA- Primary Analysis #1- 6MWT >= 200
486	Free Serum SA- Primary Analysis #2
487	Free Serum SA- Primary Analysis #2- 6MWT >= 200
488	Free Serum SA- Primary Analysis #3
489	Free Serum SA- Primary Analysis #3- 6MWT >= 200
490	Free Serum SA- Secondary Analysis
491	Free Serum SA- Secondary Analysis- 6MWT >= 200
492	Free Serum SA- Treatment Naïve Primary Analysis
493	Free Serum SA- Treatment Naïve Secondary Analysis

Table ID[(1)]	Table Description[(2)]
494	Free Serum SA- Treatment Naïve Secondary Analysis- 6MWT >= 200
495	Serum CK- Summary
496	Serum CK- Primary Analysis #1
497	Serum CK- Primary Analysis #1- 6MWT >= 200
498	Serum CK- Primary Analysis #2
499	Serum CK- Primary Analysis #2- 6MWT >= 200
500	Serum CK- Primary Analysis #3
501	Serum CK- Primary Analysis #3- 6MWT >= 200
502	Serum CK- Secondary Analysis
503	Serum CK- Secondary Analysis- 6MWT >= 200
504	Serum CK- Treatment Naïve Primary Analysis
505	Serum CK- Treatment Naïve Secondary Analysis
506	Serum CK- Treatment Naïve Secondary Analysis- 6MWT >= 200
507	HHD Lower Extremity CS vs. 6MWT Analysis
508	HHD Lower Extremity CS vs. Gait Speed Analysis
509	FAS Total Score and FAS Upper Extremity Score vs. HHD Upper Extremity CS
510	FAS Total Score and FAS Mobility Score vs. HHD Lower Extremity CS
511	FAS Total Score and FAS Mobility Score vs. 6MWT Distance
512	FAS Total Score and FAS Mobility Score vs. Gait Speed Test
513	FAS Total Score and FAS Upper Extremity Score vs. Weighted Arm Lift Test

(1) The final ICH compliant numbering schema will be completed with each delivery of planned analyses and/or final clinical study report. Numbering provided herein may be updated, without update or amendment to the SAP.
(2) Supporting Figures will be developed for most tables. The title (and brief description of type of figure) are aligned for reference in development. Figures will assume the name numbering as the primary table.