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**
Original Protocol:	**01 March 2013**
Amendment 1:	**02 October 2013**
Amendment 2:	**17 December 2014**
Amendment 3:	**07 October 2015**
Amendment 4:	**17 June 2016**

Investigational Product:	Sialic Acid-Extended Release Tablets (SA-ER)/Sialic Acid-Immediate Release Capsules (SA-IR)
Indication:	GNE myopathy, also known as Hereditary Inclusion Body Myopathy (HIBM), Distal Myopathy with Rimmed Vacuoles (DMRV), or Nonaka Disease
IND/EudraCT Number:	109,334
Sponsor:	Ultragenyx Pharmaceutical Inc. 60 Leveroni Court Novato, CA, USA 94949
Sponsor's Responsible Medical Officer:	[redacted] MD Vice President, Clinical Sciences [redacted]
Coordinating Investigator:	Professor Yoseph Caraco, MD

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

CLINICAL STUDY PROTOCOL AMENDMENT

SUMMARY OF CHANGES AND RATIONALE

UX001-CL202 Amendment 4

17 June 2016

The Protocol Amendment 3 of UX001-CL202 (dated 07 October 2015) has been modified by Amendment 4 to incorporate a number of changes based on additional information acquired since the beginning of the study. The major changes to the protocol impacting the conduct of the study are summarized below. Additional changes have also been made to provide supportive background information and rationale for the proposed changes (along with minor edits for consistency and clarity) but are not detailed in this summary.

1. The Month 36 visit was defined as the end of study visit. In addition, this amendment now provides subjects the opportunity to enroll in the UX001-CL302, an ongoing extension study. These changes affected the synopsis, Table 2.2, and Sections 7.1 and 7.5.1. This amendment also clarifies that the Termination Visit is not required for subjects who are rolling over to the UX001-CL302 extension study, but is required for subjects who terminate study participation early or who decide not to participate in the UX001-CL302 extension study.

   Rationale: The changes were made to clarify the end of study visit, clarify which subjects are required to complete the Termination Visit, and to provide subjects in the current study the opportunity to enroll in the UX001-CL302 extension study.

2. Record Retention: Section 8.4.3 has been updated to state that all study records must be retained for at least 25 years after the end of the clinical trial or in accordance with national law.

   Rationale: This administrative change has been made to reflect upcoming changes to EU clinical trial regulations and current regulations by other health authorities.

3. Updates were made to Section 7.4.2, Identity of Study Drug.

   Rationale: These changes were made for clarification.

4. A change was made to Section 8.5.4, Adverse Event Reporting to Ultragenyx.

   Rationale: This change was made to be consistent with the current Ultragenyx template language regarding this topic.

CLINICAL STUDY PROTOCOL AMENDMENT

SUMMARY OF CHANGES AND RATIONALE

UX001-CL202 Amendment 3

07 October 2015

The Protocol Amendment 2 of UX001-CL202 (dated 17 December 2014) has been modified by Amendment 3 to incorporate a number of changes based on additional information acquired since the beginning of the study. The major changes to the protocol impacting the conduct of the study are summarized below. Additional changes have also been made to provide supportive background information and rationale for the proposed changes (along with minor edits for consistency and clarity) but are not detailed in this summary.

1. Part IV was added to change the formulation from sialic acid immediate release (SA-IR) to SA extended release (SA-ER). The SA-IR dose formulation has been removed. This change affects multiple sections of the protocol synopsis and body of the protocol, including the Schedule of Events (Table 2.2), Study Rationale (Section 5.4), Study Objectives (Section 6), Investigational Plan (Section 7), and Treatments (Section 7.4).

   Rationale: By the 4th day of dosing in a nonclinical study conducted in dogs, AUC for free SA was similar between the immediate and extended release formulations. In addition, a review of population data for Month 12 of Part III in the current study confirmed that 12g/day SA-IR did not appear to provide any additional benefit compared with 6g/day SA-ER, although some individual patients may have improved. Therefore, no further SA-IR will be administered after the initiation of Part IV; patients currently on 12g/day may continue receiving the 12g/day dose, if desired, by taking SA-ER.

2. Updated Section 8.5.1 (Definition of Adverse Events) with the following text: "Note that hospitalizations planned prior to study enrollment (e.g., for elective surgeries) are not considered SAEs. Hospitalizations that occur for pre-existing conditions that are scheduled after study enrollment are considered SAEs."

   Rationale: Updated for clarification of the SAE definition.

3. Updated Sections 8.5.4 with new text related to reporting of adverse events.

   Rationale: Updated to align with other Ultragenyx protocols.

4. Updated safety contact information (Section 8.5.5).

   Rationale: Updated to inform proper reporting of serious adverse events.

CLINICAL STUDY PROTOCOL AMENDMENT

SUMMARY OF CHANGES AND RATIONALE

UX001-CL202 Amendment 2

17 December 2014

The Protocol Amendment 1 of UX001-CL202 (dated 02 October 2013) has been modified by Amendment 2 to incorporate a number of changes based on additional information acquired since the beginning of the study. The major changes to the protocol impacting the conduct of the study are summarized below. Additional changes have also been made to provide supportive background information and rationale for the proposed changes (along with minor edits for consistency and clarity) but are not detailed in this summary.

1. Sponsor's Responsible Medical Officer and associated Medical Monitor contact information (Section 8.5.6) have been updated to:

   [redacted], MD

2. Part III was added to the study design to allow for the reduction of the dose from 12g/day to 6g/day for a majority of participating subjects. This change affects multiple sections of the protocol synopsis and body of the protocol, including the Schedule of Events (Table 2.2), Study Rationale (Section 5.4), Study Objectives (Section 6), Investigational Plan (Section 7), and Treatments (Section 7.4).

   Rationale: This change is based on a review of the data for the rollover subjects from the parent study UX001-CL201 who had been receiving 12g/day in Part II of this extension study. The data analysis suggests that an improvement of at least 15% in either the UEC or the LEC after 6 months of treatment with 12g/day SA represents a response that is suggestive of an added benefit from the higher dose. The small subset of rollover subjects who meet these criteria, along with the ongoing naïve subjects, will have the option to remain on the 12g/day dose for the remainder of the study.

3. The statistical methods were updated (synopsis and Section 7.6).

   Rationale: The statistical methods were updated to reflect the changes to the study design described in change #2 and to clarify which analyses populations were used for the Part II interim analyses.

4. The protocol was updated to include a coordinating investigator. The coordinating investigator was identified on the cover page of the protocol and the selection process and responsibilities of the coordinating investigator are discussed in Investigators and Study Administrative Structure (Section 8.2).

Rationale: Identification of a coordinating investigator is required by the European Union.

5. Prohibited Medications (Section 7.4.4.1) was updated by removing the text stating that urine will be analyzed to detect the presence of ManNAc.

   Rationale: This text was removed for clarification as this study procedure was only performed in Part I.

6. Updated pregnancy text in Section 7.5.4.10.

   Rationale: This text was updated to match the current protocol template text.

CLINICAL STUDY PROTOCOL AMENDMENT

SUMMARY OF CHANGES AND RATIONALE

UX001-CL202 Amendment 1

02 October 2013

The Original Protocol 01 version of UX001-CL202 (dated 01 March 2013) has been modified by Amendment 1 to incorporate a number of changes based on additional information acquired since the beginning of the study. The majority of changes were predicated by a complete analysis and review of pharmacokinetic (PK), pharmacodynamic (PD), clinical efficacy, and safety results from the 24-week placebo-controlled, double-blind Treatment Period of the UX001-CL201 Phase 2 clinical trial. The major changes to the protocol impacting the conduct of the study are summarized below. Additional changes have also been made to provide supportive background information and rationale for the proposed changes (along with minor edits for consistency and clarity) but are not detailed in this summary.

1. **Indication:** GNE Myopathy is now the preferred term used in the protocol for the indication. The majority of references to HIBM have been replaced with GNE Myopathy.
2. **Sponsor's Responsible Medical Officer** and associated contact information has been changed to [redacted] MD PhD.
3. **Overall Study Design and Plan**.

   The study will now be conducted in two parts. Part I of the study will provide additional information on the long-term safety and efficacy of 6g/day dose of SA-ER as initially designed, except the maximum treatment duration on 6g SA-ER has been shortened to approximately 12 weeks. The Part I Termination Visit will also serve as the Baseline Visit for Part II of the study.

   Part II of the study will assess the long-term safety and efficacy of an increased SA dose (12g/day). In this phase, SA treatment will be administered in the form of SA-ER tablets and sialic acid immediate release (SA-IR) capsules. 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 GNE Myopathy subjects will be enrolled into Part II of the study. The additional subjects will provide an assessment of 12g/day SA-ER/SA-IR treatment in treatment-naïve subjects able to walk at least 200 meters (and < 80% predicted) in a screening 6 Minute Walk Test (6MWT). Throughout the Part II Treatment Period, all subjects will be administered three 500 mg SA-ER tablets and three

500 mg SA-IR capsules orally four times per day (QID), in the morning, afternoon, early evening, and at bedtime (qHS), for a total 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 (Table 2.1 and Table 2.2). If reasonable efficacy and safety are demonstrated during an interim analysis following 6 months of treatment, the subjects will continue treatment for up to 36 months. A Part II Termination Visit will be conducted 4 weeks after subjects receive their last dose of study drug.

Rationale: The modification of study design was predicated on results of planned PK, PD, clinical efficacy, and safety analyses following the 24-week placebo-controlled Treatment Period in the UX001-CL201 Phase 2 clinical study, wherein SA-ER treatment was administered at two dose levels, 3g and 6g SA-ER/day. The goal of the Week 24 interim analysis was to identify the dose that provides the best risk-benefit profile. The results show that the highest dose (6g/day SA-ER) provided sustained exposure, a modest clinical efficacy signal, and acceptable safety profile.

The clinical efficacy data showed dose-dependent improvement in muscle strength relative to placebo in some muscle groups, particularly in the upper extremities at the 6g/day SA-ER dose. These changes were statistically significant or trended towards significance, and were more pronounced in subjects that had greater walking ability at baseline, a predefined subset. Other clinical endpoints (e.g. weighted arm lift test) did not reveal measureable changes at the Week 24 interim assessment. Creatine kinase (CK) levels showed a trend to improvement in the 6g/day SA-ER dose group compared with placebo. Overall, SA-ER appeared to be well tolerated with no serious adverse events observed in either dose group.

Based on data from the Week 24 analysis following the placebo-controlled Treatment Period, the 6g/day SA-ER dose level appears to be at the lower end of the effective range, while 3g/day SA-ER had almost no effect. An additional analysis of safety and efficacy data will be conducted at the end of the Treatment Continuation Period in UX001-CL201 Phase 2 clinical study to evaluate whether the observed treatment effect is sustained or increased over a longer 48-week period. However, additional clinical benefit is not expected.

In summary, the Week 24 interim data show a modest positive clinical efficacy signal and acceptable safety profile at the 6g/day dose suggesting the potential to optimize the therapeutic index by increasing SA exposure. Therefore, investigation into optimizing the risk-benefit profile of SA substrate replacement by examining higher SA doses is warranted.

4. **Investigational Product and Treatment.**

Part II of the study will assess the safety and efficacy of 12g/day SA-ER/SA-IR treatment for 6 months. If reasonable efficacy and safety are demonstrated, the subjects will continue SA-ER/SA-IR treatment for up to 36 months.

The SA-ER/SA-IR study drugs administered in Part II of the study will consist of SA-ER tablets, each containing 500 mg of SA active ingredient in an extended release formulation, and SA-IR capsules, each containing 500 mg of SA active ingredient. During the Part II Treatment Period, the 12g total daily SA-ER/SA-IR dose will be administered by the oral route and will be divided into a QID regimen: three SA-ER tablets (1.5g SA-ER) and three SA-IR capsules (1.5g SA-IR) taken in the morning, afternoon, early evening, and qHS. If tolerability issues arise, the dose may be temporarily stepped down until symptoms resolve.

Rationale: Since successful use of SA replacement therapy in humans is believed to depend upon optimized exposure to the compound, an increased dose will be examined in Part II of the study. Although administration of more extended release tablets could be utilized, data in canines suggests that administration of immediate release SA in combination with the SA-ER will maximize absorption in the GI tract. Therefore, Part II will examine safety and efficacy of an increased dose level combining immediate release SA (SA-IR) with SA-ER.

The SA-ER/SA-IR dose and regimen for Study UX001-CL202 was selected based on the apparent detectable treatment effect at the highest dose and the association of higher SA serum levels with better improvement in strength, suggesting that a higher dose might be useful. PK data from canine studies suggest that adding immediate release SA was the most effective way to increase SA, and higher doses of SA should be safe. Supportive information is summarized below:

- **Dose effect at 6g only.** Interim results from UX001-CL201 suggest the 6g SA-ER dose level appears to be at the lower end of the effective range since a clinical efficacy signal was observed but 3g SA-ER had almost no effect.
- **The SA level correlates with treatment effect based on HHD.** The Week 24 interim data imply a positive PD signal and acceptable safety profile suggesting the potential to optimize the therapeutic index by increasing SA exposure.
- **Canine studies show that immediate release most effective way to increase SA.** Studies in normal canines showed that more than proportional increases in absorption of SA are possible if an immediate release formulation was mixed with an extended release formulation. The concept is that the immediate release product enhances stomach absorption which is not well utilized by extended release formulated tablets.
- **QID therapy should support higher SA levels.** Since SA-IR is rapidly cleared, a QID dosing regimen is predicted to provide optimized continuous exposure to SA.

Administration of a 12g total daily dose of SA would therefore be divided into 4 equal doses of 3g each (1.5g SA-ER + 1.5g SA-IR), representing only a 50% increase for each dose.

- **Safety of very high SA doses.** In a chronic toxicology study in rats, the NOAEL was 2000 mg/kg SA, which provides a safety margin of approximately 1.4-fold for the proposed 12g/day dose level. In a 6 month oral toxicity study in dogs, the NOAEL was 2000 mg/kg SA, which provides a safety margin of approximately 5-fold for the human 12g/day dose level.
- **Single doses of 6g SA-ER given in one dose, were well tolerated.** In the Phase 1 PK and tolerability study, 6g SA-ER was administered to GNE Myopathy subjects in a single oral dose and was well tolerated with no SAEs observed.

5. **Study Objectives.**

The safety objectives in Part II of the study have been modified to evaluate the safety of 12g/day SA in the treatment of GNE Myopathy subjects over a 6 month period.
The clinical efficacy objectives of the study remain unchanged, except to reflect the change in investigational product to SA-ER/SA-IR. An additional exploratory objective has been added to determine whether 12g /day of SA-ER/SA-IR administered as 1.5g/1.5g four times per day is superior to prior treatment with 6g/day of SA-ER therapy administered as 2g three times per day in GNE Myopathy subjects.

Rationale: The objectives of the study have been revised to delineate specific aims for Part I and Part II of the study. The change is in agreement with the overall study design and treatment regimens.

6. **Selection of Study Population and Sample Size.**

The sample size has been increased to enroll an additional 10 treatment naïve GNE Myopathy subjects into Part II of the study.

Rationale: Approximately 46 subjects currently enrolled in the study have completed a minimum of 48-weeks SA-ER treatment as part of study UX001-CL201 and Part I of this study. Part II of the study will be the first time GNE Myopathy subjects will be treated with 12g/day SA-ER/SA-IR. Therefore, 10 additional subjects will be enrolled to assess safety and clinical efficacy of the higher 12 g/day dose level in a treatment naïve population.

7. **Inclusion Criteria.**

The first inclusion criterion was modified to:

- Enrollment in, and successful completion of the UX001-CL201 protocol **OR** (for 10 treatment naïve subjects):
  - Have a confirmed diagnosis of GNE Myopathy
  - Aged 18 -65 years of age, inclusive
  - Able to walk ≥ 200 meters and < 80% of predicted normal during the 6MWT (orthotics and assistive devices allowed)
  - No prior history of treatment with SA or MaNAc

Rationale: The modified criterion aids in defining the study population, which consists primarily of GNE Myopathy subjects who completed the UX001-CL201 Phase 2 clinical study, but also defines requirements for the enrollment of additional treatment naïve subjects. The diagnosis and age range for the treatment naïve subjects are the same as requirements for continuing subjects. The ability to walk at least 200 meters during the 6MWT was an enrollment target for 60% of subjects in the UX001-CL201 protocol. Since the strongest clinical efficacy signal in the Week 24 interim analysis was observed in this subset of GNE Myopathy subjects, Part II of this study will seek to enroll additional subjects most likely to obtain clinical benefit from treatment.

8. **Schedule of Events**.

For clarity, the Schedule of Events has been separated into two distinct tables. The visit schedule and assessments to be conducted during Part I of the study are presented in Table 2.1. The visit schedule and assessments to be conducted during Part II of the study are presented in Table 2.2.

Rationale: Specific assessments may differ depending on the phase of the study (i.e. Part I or Part II). Evaluations of safety, changes in clinical endpoints such as muscle strength, mobility, and function, PK, and changes in exploratory serum biomarkers will be performed according to the Schedule of Events specific to each phase of the study.

9. **Exploratory Efficacy Measures**.

Exploratory efficacy assessments will be conducted as indicated in the Schedule of Events for Parts I and II of the study (Table 2.1 and Table 2.2, respectively). However, samples to assess serum protein biomarkers (other than CK) will not be obtained in Part II of the study.

Rationale: Results from a panel of serum biomarkers at the Week 24 interim analysis of the Phase 2 study (UX001-CL201) were ambiguous. Therefore, serum protein biomarkers will not be assessed in Part II of the study to avoid subjecting study participants to unnecessary procedures. CK levels in serum will be assessed in both Parts

I and II of the study since a positive, dose-dependent decrease in serum CK levels was observed in UX001-CL201.

10. **Safety Measures & Procedures**.

A detailed medical history, including a GNE Myopathy-specific medical history will be obtained at the Part II Screening/Baseline Visit for newly enrolled subjects only.
There are no changes to safety measures, only revised timing of assessments.
Safety assessments will be conducted as indicated in the Schedule of Events for Parts I and II of the study (Table 2.1 and Table 2.2, respectively).

Rationale: For continuing subjects, the Medical History information obtained during the UX001-CL201 study will carry over to the current treatment extension study.
Similar information must be obtained for the treatment naïve subjects who will enroll directly into Part II of the study.

Stopping Rules.

Specific language regarding stopping rules (Section 7.3.3.1) has been modified as follows:

*"If two subjects develop the same **unexpected** Grade 3 AE that is possibly or probably related to study drug or any subject develops an **unexpected** Grade 4 AE that is possibly or probably related to study drug, enrollment of new subjects ~~will~~ **may be** suspended until a thorough evaluation can be performed."*

Rationale: Interim results following a 24-week Treatment Period with SA-ER are now available and provide a profile of expected AEs; no SAEs have been reported to date in the ongoing study. Should unexpected Grade 3 and 4 AEs occur as detailed above, a full clinical evaluation will performed by the medical monitor, principal investigators, and the Data Monitoring Committee (DMC) as detailed in the protocol. Following the full evaluation, an informed decision can be made whether to suspend enrollment or stop the study.

Safety Contact Information.

The safety contact information for Ultragenyx (Biosoteria/Dohmen Safety) has been updated.

11. **Drug Concentration Measurements.**

Free SA in the urine will be measured in Part I of the study only. Free SA trough levels will be assessed in serum during Parts I and II of the study. There will be no assessments of free SA in the urine during Part II of the study.

Rationale: Results of PK assessments at the Week 24 interim analysis of the Phase 2 study (UX001-CL201) suggest serum SA measurement is more reliable than urine for characterizing trough levels of SA. Therefore, urine PK parameters will not be assessed in Part II of the study to avoid subjecting study participants to unnecessary procedures.

12. **Statistical Methods.**

An interim analysis will be conducted when the last subject has completed the Month 6 Visit of the Part II Treatment Period. For Part II efficacy evaluation of the continuing subjects, change from baseline of Part II to Month 6 assessment at 12g/day SA-ER/SA-IR dose will be determined and compared with the improvement observed during the first 6 months of treatment with 6g/day SA-ER dose and to the rate of change observed with placebo or 3g treatments during the first 6 months of the study. The 10 additional treatment naïve subjects will be evaluated for change from their baseline visit to Month 6 assessment at 12g/day SA-ER/SA-IR dose compared with placebo, 3 g and 6 g treatments for 24 weeks in subjects that walk more than 200m at baseline in the 6MWT.

Rationale: Changes to the planned statistical analysis are consistent with the modified study design to assess the efficacy and tolerability of the higher dose of sialic acid. The planned interim analysis following 6-months treatment with SA-ER/SA-IR will provide an initial assessment of safety and efficacy. If reasonable safety and efficacy are demonstrated, subjects will continue therapy for up to 36 months. Full details of planned analysis will be presented in the Statistical Analysis Plan for UX001-CL202.

2 SYNOPSIS

TITLE OF STUDY:
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

STUDY SITES:
Four sites, globally

PHASE OF DEVELOPMENT:
Phase 2

RATIONALE:
GNE myopathy or hereditary inclusion body myopathy (HIBM) is a rare and severely debilitating disease caused by a defect in the biosynthetic pathway for sialic acid (SA). Substrate replacement of SA in an extended release formulation (SA-ER; also termed Ace-ER) is a potential therapeutic strategy based on evidence from relevant *in vivo* models, supported by pharmacokinetic (PK) characterization in a Phase 1 clinical study, and stabilization in muscle strength in a Phase 2 randomized controlled trial (UX001-CL201). The interim data from the Phase 2 study implied a positive clinical efficacy signal and acceptable safety profile suggesting the potential to optimize the therapeutic index by increasing SA exposure. Since successful use of SA replacement therapy in humans is believed to depend upon optimized exposure to the compound, an increased dose was suggested. Although administration of more extended release tablets could be utilized, data in canines suggest that administration of immediate release SA (SA-IR) in combination with the SA-ER will maximize absorption in the GI tract. Therefore a study testing an increased dose level combining SA-IR with SA-ER was proposed.

Subjects completing the 48-week study (UX001-CL201) were eligible to continue treatment under this open-label extension protocol. Additional GNE Myopathy subjects have been enrolled to assess the safety and efficacy of SA-ER/SA-IR in a treatment naïve population.

Ultragenyx is conducting this study (UX001-CL202) in four 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 long-term safety and efficacy of 12g/day SA (comprised of 1.5g of SA-ER and 1.5g of SA-IR treatment 4 times per day). Parts III and IV will provide long-term safety and efficacy data on both 6 and 12g/day SA (both SA-ER/SA-IR [Part III] and SA-ER [Part IV]). Part III was added based on a review of individual subject data for the rollover subjects from the parent study UX001-CL201 at Month 6. The data analysis suggested that a small subset of subjects received an added benefit from the higher dose (defined as at least a 15% increase in either the UEC or LEC). The rollover subjects who met these criteria, along with the ongoing naïve subjects, had the option to remain on the 12g/day dose for the remainder of the study. Part IV was added to change the formulation from SA-IR to SA-ER. The SA-IR dose formulation has been removed based on data showing that by the 4th day of dosing in a nonclinical study conducted in dogs, AUC for free SA was similar between the immediate

and extended release formulations. In addition, a review of population data for Month 12 of Part III in the current study confirmed that 12g/day SA-IR did not appear to provide any additional benefit compared with 6g/day SA-ER, although some individual patients may have improved. Therefore, no further SA-IR will be administered after the initiation of Part IV; patients currently on 12g/day may continue receiving the 12g/day dose, if desired, by taking SA-ER.

Patients who elect to decrease from 12g/day to 6g/day may be allowed to do so upon Sponsor approval.

OBJECTIVES:

The safety objectives of the study are to:

- 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 (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 (Part II) over a 6 month treatment period.
- Evaluate the safety of SA treatment at both 6g/day and 12g/day (Part III [SA-ER/SA-IR] and Part IV [SA-ER]).

The clinical objectives of the study are to:

- Evaluate the long-term effect of SA treatment of GNE Myopathy subjects on muscle strength as measured by hand-held dynamometry (HHD)
- Evaluate the long-term effect of SA treatment of GNE Myopathy subjects on mobility, strength, and function using a series of physical performance measures
- Evaluate the long-term effect of SA treatment of GNE Myopathy subjects on functional disability using an interview-based questionnaire.

The exploratory objectives of the study are to:

- Evaluate the effect of SA 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)
    - Determine whether a subset of subjects have additional benefit on the higher dose treatment.

STUDY DESIGN AND METHODOLOGY:

This open-label extension study of will assess the long-term safety and efficacy of SA treatment over a period of approximately 36 months, or until marketing approval or program termination by Ultragenyx. Subjects who complete the study will be eligible to enroll into UX001-CL302 open-label extension study. 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.

Beginning with the Part II-Baseline Visit, all subjects currently enrolled in Part I will crossover to the SA-ER/SA-IR dosing regimen. Approximately 10 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).

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 (Table 2.1 and Table 2.2). A Termination Visit will be conducted 4 weeks after subjects receive their last dose of study drug (last dose of study drug received at Month 36). For subjects who are eligible and choose to participate in the UX001-CL302 open-label extension study, the Month 36 Visit is considered the end of study visit and the Termination Visit is not required. Any subject who discontinues the current study early or is ineligible or decides not to participate in the UX001-CL302 open-label extension study is required to have a Termination Visit 4 weeks after their last dose of study drug, as per Schedule of Events. Efficacy data analyses will be conducted at the end of the Treatment Period, although interim analyses may be performed 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 Serious Adverse Events (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.

NUMBER OF SUBJECTS PLANNED:

Up to 46 subjects previously treated in the UX001-CL201 study will be enrolled. Approximately 10 subjects, naïve to SA and MaNAc treatment, will be enrolled directly into Part II of the study.

DIAGNOSIS AND CRITERIA FOR INCLUSION AND EXCLUSION:

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

- Enrollment in, and successful completion of the UX001-CL201 protocol **OR**
  (for 10 treatment naïve subjects):
  - Have a confirmed diagnosis of GNE Myopathy
  - Aged 18 -65 years of age, inclusive
  - Able to walk ≥ 200 meters and < 80% of predicted normal during the 6MWT (orthotics and assistive devices allowed)
  - No prior history of treatment with SA or MaNAc
- Must be willing and able to provide written, signed informed consent after the nature of the study has been explained, and prior to any research-related procedures
- Must be willing and able to comply with all study procedures
- Sexually active subjects must be willing to use an acceptable method of contraception while

participating in the study

- Females of childbearing potential must have a negative pregnancy test at Baseline and be willing to have additional pregnancy tests during the study. Females considered not of childbearing potential include those who have been in menopause for at least two years, or have had tubal ligation at least one year prior to Baseline, or who have had total hysterectomy.

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

- Pregnant or breastfeeding at Baseline or planning to become pregnant (self or partner) at any time during the study
- Use of any investigational product (other than SA-ER tablets) to treat GNE Myopathy
- Ingestion of N-acetyl-D-mannosamine (ManNAc) or similar SA-producing compounds
- Has had any hypersensitivity to SA or its excipients that, in the judgment of the investigator, places the subject at increased risk for adverse effects
- Have any co-morbid conditions, including unstable major organ-system disease(s) that in the opinion of the investigator, places the subject at increased risk of complications, interferes with study participation or compliance, or confounds study objectives.

INVESTIGATIONAL PRODUCT, DOSE AND MODE OF ADMINISTRATION:

Part I: The investigational product will consist of SA-ER tablets, each containing 500 mg of SA active ingredient in an extended release formulation. During the Part I Treatment Period, the 6000 mg (6g) total daily SA-ER dose will be administered by the oral route and will be divided into a TID regimen: four tablets in the morning, four tablets in the early evening, and four SA-ER tablets qHS.

Part II: Each dose of SA-ER/SA-IR will consist of SA-ER tablets, each containing 500 mg of SA active ingredient in an extended release formulation and SA-IR capsules, each containing 500 mg of SA active ingredient. During the Part II Treatment Period, the 12,000 mg (12g) total daily SA dose will be administered by the oral route and will be divided into a QID regimen: three SA-ER tablets (1.5g SA-ER) and three SA-IR capsules (1.5g SA-IR) taken in the morning, afternoon, early evening, and qHS. If tolerability issues arise, the dose may be temporarily stepped down until symptoms resolve.

Part III: 12g/day dose – Each dose of SA-ER/SA-IR will consist of SA-ER tablets, each containing 500 mg of SA active ingredient in an extended release formulation and SA-IR capsules, each containing 500 mg of SA active ingredient. During the Part III Treatment Period, the 12,000 mg (12g) total daily SA dose will be administered by the oral route and will be divided into a TID or QID regimen. If tolerability issues arise, the dose may be temporarily stepped down until symptoms resolve.

6g/day dose – Each dose of SA-ER will consists of tablets, each containing 500 mg of SA active ingredient in an extended release formulation. During the Treatment Period, the 6000 mg (6g) total daily SA-ER dose will be administered by the oral route and will be divided into a TID regimen.

Part IV: 6g/day dose and 12g/day dose – Each dose of SA-ER will consists of tablets, each containing 500 mg of SA active ingredient in an extended release formulation. During the Treatment Period, the 6g total daily SA-ER dose will be administered by the oral route and will be divided into a TID

regimen. The 12g total daily SA-ER dose will be administered by the oral route and will be divided into a TID or QID regimen.

All doses should be taken with food (i.e. within 30 minutes following a meal or snack).

DURATION OF TREATMENT:

The Part I Treatment Period will be up to approximately 12 weeks (3 months) in duration. The Part II, Part III, and Part IV Treatment periods will be up to 36 months in duration. The total duration of the study will be up to 40 months.

CRITERIA FOR EVALUATION:

Efficacy:

Efficacy will be evaluated by continued improvement in clinical assessments. Efficacy assessments may differ depending on the phase of the study (i.e. Part I, Part II, Part III, or Part IV). For Part I efficacy evaluation, results from the last pre-treatment assessment from UX001-CL201 will be compared with the last post-treatment assessment for the Part I Treatment Period as listed in the Schedule of Events (Table 2.1), with efficacy conclusions based on change since SA-ER treatment initiation.

An interim analysis will be conducted when a majority of subjects have completed the Month 6 Visit of the Part II Treatment Period. For Part II efficacy evaluation of the continuing subjects, change from baseline of Part II to Month 6 assessment at 12g/day SA-ER/SA-IR dose will be determined and compared with the improvement observed during the first 6 months of treatment with 6 g/day SA-ER dose, and to the rate of change observed with placebo or 3g treatments during the first 6 months of the study. The changes from baseline of the treatment-naïve subjects will be evaluated over time.
In addition, changes in muscle strength over the entire treatment period of subjects who started with 6g/day and 3g/day will be evaluated and compared to the projected values of subjects who received placebo for the first 24 weeks of treatment in UX001-CL201.

Clinical Efficacy Measures:

- Hand-Held Dynamometry: 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 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: 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: 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 on normative data.
- Weighted Arm Lift Test: 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: 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.

Exploratory Efficacy Measures:

- Serum protein markers: Serum specimens will be evaluated to assess potential use as biomarkers of sialylation.
- Creatine kinase levels in serum will be assessed as a potential biomarker for muscle injury

Safety:

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

- Vital signs
- Neurological and physical examination results
- Laboratory evaluations
- Interval history: reported symptoms of increasing muscle weakness or pain, incidence of falls

STATISTICAL METHODS:

Details of the planned interim analysis, safety and efficacy analyses will be provided in a statistical analysis plan maintained separately from this protocol.

Interim Analysis:

An Interim analysis will be conducted when a majority of subjects have completed the Month 6 Visit during the Part II Treatment period.

Efficacy Analyses:

Efficacy data analyses will be conducted at the end of the 6-month Treatment Period with SA-ER/SA-IR, when all subjects have completed 12 months of participation, and at the end of the 36 month Treatment Period. The treatment naïve subjects will be studied as a separate subgroup.

Clinical efficacy analyses will include: 1) Muscle strength as measured by HHD, 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, 4) Arm raising ability as measured by the weighted arm lift test, which will be reported as the total number of completed repetitions, and 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.

For those clinical evaluations with repeated assessments (i.e., HHD, 6MWT, and the walking speed and weighted arm lift tests), the analysis will be performed using a repeated measures analysis.

A full accounting of the analyses for Parts III and IV of the study will be provided in the Statistical Analysis Plan.

Safety Analyses:

All subjects who receive study drug will be included in the safety analysis. Safety will be evaluated on the incidence and frequency of AEs and SAEs, and clinically significant change in vital signs, laboratory test results, or physical examinations. Safety data will be periodically reviewed by the DMC.

Table 2.1: 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 2.2: Schedule of Events (Parts II, III, and IV)

Assessments and Events	Parts II, III, and IV Treatment Period [b] (months)														Term Visit [c]
	Screening/ Baseline [a]	1	3	6	9	12	15	18	21	24	27	30	33	36[k]	
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 also serves as the Parts II, III, and IV Baseline Visit for continuing subjects. SA naïve subjects enter directly into Part II of the study (Screening/Baseline Visit for these subjects). Study drug will be dispensed only after UX001-CL202 (Parts II, and III, and IV) consent has been signed.

[b] The Month 1 Visit window is ± 1 week. For all other Visits the window is ± 14 days. For Part III and Part IV transitions, subjects will be asked to return to the clinic (may be an unscheduled visit) within 5 weeks from IRB/EC approval, to discuss their dosing and to consent.

[c] The 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. The Termination Visit is not required for subjects who are eligible and choose to participate in the UX001-CL302 open-label extension study, but must be completed for any subject who terminates study participation early or is ineligible or decides not to participate in the extension study.

[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.

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

[i] 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.

[k] Subjects who complete this study and are eligible may enroll in the UX001-CL302 open-label extension study. The Month 36 Visit is considered the end of study visit for subjects who are eligible and chose to participate in the open label extension study.

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4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviations

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
CSR	clinical study report
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
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
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
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
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SOC	System Organ Class
TID	three times per day
US	United States
WBC	white blood cell

Definition of Terms

Investigational Product is defined as, "A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use" (from International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use [ICH] Harmonised Tripartite Guideline E6: Guideline for Good Clinical Practice).

The terms "Investigational Product" and "study drug" may be used interchangeably in the protocol.

5 INTRODUCTION

Sialic Acid-Extended Release (SA-ER, UX001; also termed Ace-ER) is an extended release formulation of sialic acid (SA, also known as N-acetylneuraminic acid or NANA) intended as a substrate replacement therapy for GNE myopathies. GNE myopathy, hereditary inclusion body myopathy (HIBM), distal myopathy with rimmed vacuoles (DMRV), and Nonaka disease are all different names of the same disorder, which is caused by a defect in the biosynthetic pathway for SA. For the purposes of this protocol, GNE Myopathy will be used as the term for this disorder.

Patients with GNE Myopathy cannot produce sufficient SA in muscle tissues; consequently glycoproteins and glycolipids in affected patients are not appropriately sialylated.
In humans, GNE Myopathy is a severe progressive myopathy with onset usually in affected patients 18-30 years of age. Initial diagnosis is followed by progressive loss of muscle strength, distal to proximal, which ultimately leads to loss of ambulation in 10-20 years.
By replacing SA substrate, sialylation should be restored on key target glycoproteins and glycolipids and should lead to restoration of biochemical function, improved muscle physiology, and improved clinical function.

The scientific rationale for this substrate replacement therapy is primarily based on the nature of the underlying genetic disease and on the work of Malicdan and colleagues, who demonstrated oral SA replacement therapy can be effective in restoring biochemical function with higher levels of sialylation in a relevant HIBM mouse model (Malicdan et al. 2009). The improved biochemical function in treated mice resulted in reduced or absent HIBM pathology, prevented clinical signs of muscle disease, and improved survival (Malicdan et al. 2009).

SA has a short half-life in the circulation. Rapid clearance makes it difficult to use as a therapeutic replacement substrate in which a steady and constant supply of SA is required for use in glycoprotein and glycolipid synthesis. The SA-ER formulation is expected to provide more stable blood levels of SA without spikes or troughs over the 24 hour cycle in humans when dosed three or four times per day (TID or QID). Continuous exposure is likely an important step in assuring adequate sialylation during peak periods of synthesis, particularly during the night when maximal muscle growth and repair occur.

The safety of SA has been evaluated in studies of chronic treatment of HIBM mice and in toxicology studies in multiple species of normal animals. Data from these studies, summarized in the Investigator's Brochure (IB), established a reasonable safety profile for SA and allow the determination of a no observed adverse effect level (NOAEL), setting the stage for the translation of this work to human GNE Myopathy patients.

The SA-ER formulation was evaluated in a Phase 1 pharmacokinetic (PK) study to assess safety and exposure after a single dose and seven days of repeat dosing in SA-deficient GNE Myopathy subjects. Data from this study suggests SA-ER is well tolerated by subjects with GNE Myopathy at single and multiple doses up to 6g/day, and sustained levels of SA in

blood and urine are achieved. The TID dosing interval is sufficient to maintain trough levels of SA above background.

A Phase 2 randomized, double-blind study has been performed to evaluate the safety and pharmacodynamic (PD) effects of SA-ER at two dose levels (6g/day and 3g/day) over 48 weeks, including a 24-week placebo-controlled Treatment Period followed by a 24-week Treatment Continuation period on SA-ER. Interim results from the 24-week placebo controlled Treatment Period implied a clinical efficacy signal and acceptable safety profile suggesting the potential to optimize the therapeutic index by increasing SA exposure.

Part I of the study will provide treatment continuation for subjects completing the aforementioned Phase 2 study and elicit additional information on the long-term safety and efficacy of 6g/day SA-ER. Parts II, III, and IV of the study will assess the long-term safety and efficacy of 12g/day SA-ER/SA-IR or SA-ER treatment (1.5g/1.5g TID or QID) and the long-term safety and efficacy of 6g/day SA-ER treatment (1.5g TID) for up to 36 months.

Ultragenyx is also sponsoring a GNE Myopathy-Disease Monitoring Program (GNEM-DMP), a novel registry/natural history study to obtain data on the disease characteristics of GNE Myopathy and its progression.

5.1 Overview of the Disease

GNE Myopathy was first described by Argov and Yarom in 1984 in a group of affected Iranian Jews in Israel (Argov et al. 1984). The patients showed progressive muscle weakness and atrophy, and rimmed vacuoles on biopsy. Since that time, a variety of GNE Myopathy patients have been identified worldwide, including those of Italian, Japanese, Thai, Indian, American and African origin (Huizing et al. 2009). The clinical course is similar among these populations, and includes disease onset usually after age 20 years (mean 26 years, range 15–40 years; (Nalini et al. 2010); (Nonaka et al. 2005); (Sadeh et al. 1993); (Sunohara et al. 1989) though it can be symptomatic earlier.

Patients often have foot drop due to tibialis anterior weakness as a first sign of GNE Myopathy; general weakness is usually more pronounced peripherally, which then progresses proximally. Both weakness and atrophy are noted in muscles, with some fatty replacement infiltration as the disease advances. In many patients, there is a curious relative sparing of the quadriceps for unknown reasons. The forearm flexors and axial musculature may become more involved over time. The rate of progression is gradual and variable between patients over a 10–20 year period leading to a wheelchair-bound state in a mean of 12 years (Nonaka et al. 2005). The ocular, pharyngeal and respiratory muscles are relatively spared clinically though they may show some abnormal pathology in some patients (Argov et al. 1984). A representative example of disease progression was chronicled in Japanese patients over a decade (Sunohara et al. 1989) and showed the Medical Research Council (MRC) scale of manual motor assessment scores on a five point scale declining over a decade or so in three patients. Disease progression is not rapid compared with some

myopathies but ultimately the level of function becomes severely compromised and equivalent to quadriplegia.

Other clinical or physiological evaluations of GNE Myopathy patients show a variable number of abnormalities, all consistent with the myopathic pathologic process. Unlike other myopathies, blood creatine kinase (CK) activities are only mildly elevated or remain in the normal range (22/58 patients reported by three publications had two-times or higher elevations; (Sadeh et al. 1993); (Mizusawa et al. 1987); (Sunohara et al. 1989) but evaluation of CK may still be useful as a marker for GNE Myopathy. The mouse model of HIBM showed elevated CK levels that improve substantially on treatment (Malicdan et al. 2009). The decline in muscle bulk and function is substantial but the time course of decline may be sufficiently slow as to not cause acute CK elevations as observed in other disorders, such as Duchenne muscular dystrophy.

Electromyography (EMG) in GNE Myopathy patients is abnormal, with spontaneous fibrillations consistent with denervation. A myopathic pattern (polyphasic muscle unit action potentials [MUAPs]) consistent with denervation is observed, however nerve conduction is generally normal (Sadeh et al. 1993); (Mizusawa et al. 1987). Conducting EMG in clinical programs is very difficult as there are substantial difficulties with differences in operators and inconsistencies of findings.

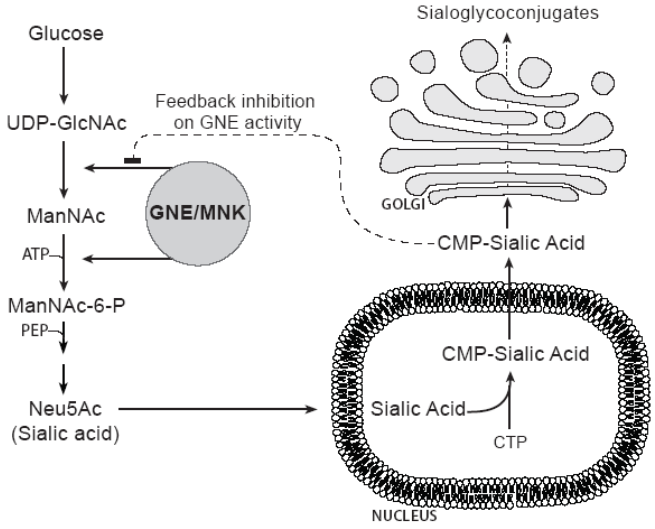
Imaging studies of the muscle by computed tomography (CT) scan (Sadeh et al. 1993); (Mizusawa et al. 1987) or magnetic resonance imaging (Huizing et al. 2009) show substantial and diffuse abnormalities to muscle structure with significant fat infiltration in affected muscles but the quadriceps have more normal appearance (Huizing et al. 2009). Many muscles have limited muscle tissue left, which could impact the potential for optimal treatment and substantial disease reversal in advanced patients.

All GNE myopathies (HIBM, DMRV and Nonaka disease) are caused by defects in the GNE gene encoding the enzyme for the first step of the SA biosynthetic pathway (Figure 5.1.1). The GNE gene codes for the bifunctional enzyme glucosamine (UDP-N-acetyl)-2-epimerase/N-acetylmannosamine kinase (GNE/MNK) (Eisenberg et al. 2001); (Jay et al. 2009). The enzyme is the rate-controlled and regulated first step in the biosynthesis of the SA that is required for the complete glycosylation of many glycoproteins and glycolipids.

Studies in tissues and mouse models have shown that the deficiency of SA production in GNE Myopathy is a key factor in the disease state, though the exact pathophysiologic effect of decreased sialylation on glycoproteins or glycolipids is still debated. Sialylation is decreased in the most credible experiments and effects on proteins like neural cell adhesion molecule (NCAM) or on proteases like neprilysin, have been proposed (Malicdan et al. 2008); (Broccolini et al. 2009). NCAM is essential for muscle enervation and is hyposialylated in GNE Myopathy (Ricci et al. 2006). The pattern of spontaneous fibrillation of denervation in GNE Myopathy may be consistent with a pathophysiological role for NCAM hyposialylation (Broccolini et al. 2009). NCAM hyposialylation was used recently

to identify atypical GNE Myopathy patients with GNE mutations among a cohort of myopathy patients (Broccolini et al. 2010). Another model involves a hyposialylation effect on neprilysin, an endopeptidase for hydrophobic proteins. The accumulation of unfolded proteins and amyloid is consistent with neprilysin being deficient (Malicdan et al. 2008). When hyposialylated, neprilysin is less stable and less active, potentially leading to the accumulation of unfolded, undigested proteins in vacuoles (Broccolini et al. 2008). Among glycolipids, GM3 is also decreased in GNE Myopathy but the role this glycolipid plays in the biology of the disease is not clear (Paccalet et al. 2010). Even with these limitations as to the specific pathophysiological role of sialylation, analyses of sialylation of these muscle components should still be useful in assessing the PD effects of substrate replacement therapy.

Figure 5.1.1: The Sialic Acid Biosynthetic Pathway



Although no proven pathway for the effect of hyposialylation in GNE Myopathy has been demonstrated conclusively, the pathology and data suggest that some combination of pathophysiologies is likely and that human skeletal muscle is prone to these problems because of normally lower expression levels of GNE/MNK. In any case, replacement with either N-acetyl-D-mannosamine (ManNAc), which is located downstream of the block in GNE/MNK, or SA itself can restore CMP-SA synthesis and subsequent sialylation of proteins and lipids (Figure 5.1.1). The GNE/MNK protein may have other functions, but the substrate replacement work to date shows that its role in the synthesis of SA is its dominant role in the muscle cell and SA deficiency is at the core of the cause of this disease.

5.2 Brief Overview of the Development of the Product

A brief overview of existing information is provided below; a comprehensive review of the data is contained in the IB provided by Ultragenyx Pharmaceutical Inc. (Ultragenyx), which should be reviewed prior to initiating the study.

SA as an active ingredient was produced from N-acetylglucosamine using an enzyme catalyzed process. The active ingredient was subjected to a series of nonclinical pharmacology and toxicology studies conducted by Ultragenyx; evaluation of the active ingredient also included some data from prior published work on SA toxicology. The NOAEL for the product was determined to be 2000 mg/kg in dogs and rats. SA-ER, the extended release formulation of SA to be used in the study, was developed to enhance the PK of the product due to its rapid clearance from the body.

Following clearance of an Investigational New Drug (IND) submission by the United States (US) Food and Drug Administration (FDA), a Phase 1 study of SA-ER was conducted. Over a range of single or multiple day doses from 650 - 6,000 mg/day no safety problems were identified, and PK analysis showed acceptable absorption of the product with a PK curve that covered about 8-16 hours. Repeat dosing for one week with dose levels from 1,950-6000 mg/day showed that trough levels could be maintained above the background level, as expected for a sustained release formulation.

A Phase 2 randomized, placebo-controlled study has been performed to evaluate the safety and PD effects of SA-ER at two dose levels (6g/day and 3g/day). The study consisted of a 24-week placebo-controlled Treatment Period, followed by an additional 24-week Treatment Extension period with all subjects on the investigational product. The interim 24-week data from the Phase 2 study suggested a positive clinical efficacy signal and acceptable safety profile indicating the potential to optimize the therapeutic index by increasing SA exposure.

5.2.1 Brief Description of the Investigational Product

SA (also known as N-acetylneuraminic acid or NANA) intended as a substrate replacement therapy for GNE Myopathy, which is caused by a defect in the de novo biosynthesis of sialic acid. The choice of an extended release formulation is based on the fact that SA has a short half-life in the circulation and its rapid clearance makes it difficult to use as a therapeutic replacement substrate in which a steady and constant supply of SA is needed. SA-ER was developed to improve the stability of exposure to SA and allow more appropriate dosing and efficient substrate replacement.

SA-ER 500 mg tablets are white to off-white, uncoated or film-coated, extended release, oval tablets that are designed for oral administration. The tablet formulation contains approximately 43.3% active pharmaceutical ingredient in a mixed polymer matrix developed for extended release of SA over 24 hours. Tablets are manufactured by a formulation process using wet aqueous granulation; the blend is then dried and compressed into tablets. Film-coated tablets are coated with Opadry II, a non-functional aqueous film coating. SA-ER 500 mg tablets are 1,150 mg in total weight.

Since successful use of SA replacement therapy in humans is believed to depend upon optimized exposure to the compound, an increased dose was examined in Part II of this extension study. Although administration of more extended release tablets could have been utilized, data in canines suggested that administration of immediate release SA in

combination with the SA-ER would maximize absorption in the GI tract. Therefore a study testing an increased dose level combining immediate release SA (SA-IR) with SA-ER was proposed in Amendment 1. Amendment 2 allows for subjects to receive either 6g/day or 12g/day based on the data collected and analyzed from Part II. Refer to Section 7.2 for additional details and rationale for the dose reduction in Part III.

SA-IR 500mg capsules are naturally colored, size 000, immediate release, hard gelatin capsules designed for oral administration. The capsule formulation contains approximately 93.5% active pharmaceutical ingredient. Manufacturing consists of dry blending followed by filling into capsules. SA-IR capsules have a fill weight of approximately 535 mg and a total weight of approximately 698 mg.

5.2.2 Nonclinical Studies

Published in vivo studies in the HIBM mouse model have shown that replacement by SA can reduce muscle weakness and atrophy, improve muscle pathology and function, and restore sialylation in muscle (Malicdan et al. 2009). The rational basis for the use of SA as a therapy in GNE Myopathy is primarily dependent on these results. Key safety pharmacology, PK, and toxicology studies to support the use of SA in treating GNE Myopathy are summarized below; additional details may be found in the IB.

Safety pharmacology: Ultragenyx conducted the core battery of safety pharmacology studies of SA that are recommended by ICH guidelines. These studies consisted of in vitro human ether-à-go-go-related gene (hERG) channel inhibition, neurobehavior in rats, and respiratory and cardiovascular evaluations in dogs after oral administration of SA. SA did not show any potential for QT prolongation in the hERG assay at concentrations as high as 6 x 10-3 mole/L. There were no adverse effects on neurobehavior in rats or on respiratory and cardiovascular function in dogs at oral SA doses as high as 2000 mg/kg.

PK study in dogs: Ultragenyx conducted a multiple-dose, cumulative dosing, PK study in dogs to assess exposure following administration of SA-ER and the SA-ER/SA-IR treatment combination. Each dog was administered SA-ER (200 mg/kg/day; human dose equivalent 100 mg/kg/day) TID throughout the study duration (12 days). Following 4 days of SA-ER treatment, SA-IR (100 mg/kg/day) TID was added to SA-ER treatment. Following 4 days of SA-ER/SA-IR treatment, the SA-IR dose was increased to 200 mg/kg/day. The highest dose level of SA-ER/SA-IR was equivalent to a human dose of 200 mg/kg/day. The area under the curve (AUC) during the 8-hr dosing window increased proportionally to the dose of SA-IR, suggesting the administration of SA in extended-release and immediate-release forms can improve overall absorption of SA-ER and increase free SA levels up to 3X in the serum. Overall SA-ER/SA-IR was well tolerated in this study.

Chronic toxicology studies in rats and dogs: In an oral 6-month rat study, there were no treatment-related effects on clinical condition, body weight, food consumption, ophthalmology, clinical pathology (hematology, blood chemistry, and urinalysis) and in pathologic evaluations (gross, organ weight, and histopathology). The no observed adverse

effect level (NOAEL) in this study was 2000 mg/kg which is equivalent to approximately a 17 g daily human dose. This provides a safety margin of approximately 1.4–fold over the proposed highest dose (12g/day) in the Phase 2 UX001-CL201 Study. The 9-month oral toxicity study in dogs did not show any adverse effects on clinical condition, body weight, food consumption ophthalmology, electrocardiography, clinical pathology (hematology, blood chemistry, and urinalysis) and in pathologic evaluations (gross, organ weight, and histopathology). The NOAEL in this study was 2000 mg/kg which is equivalent to a 60 g daily human dose. This provides a safety margin of approximately 5–fold over the proposed highest dose (12g/day) proposed in the Phase 2 UX001-CL201 Study.

Reproductive and developmental toxicology studies in rats and rabbits: To date, reproductive and developmental toxicity studies at oral doses as high as 2000 mg/kg/day have not shown any adverse effects on fertility of male or female rats, or treatment-related effects on pregnant females or embryo-fetal development parameters in rats and rabbits.

5.2.3 Previous Clinical Studies

Key results from studies to support the use of SA in treating GNE Myopathy are summarized below; additional details may be found in the IB.

Phase 1 PK and Safety (UX001-CL101): *"A Phase 1 Study to Evaluate the Safety and Pharmacokinetics of Single and Repeat Doses of Sialic Acid Extended-Release (SA-ER) Tablets in Patients with Hereditary Inclusion Body Myopathy (HIBM)"*.

The study was conducted in 28 subjects who received single and multiple doses to assess the PK and safety of SA-ER. Subjects received SA-ER tablets orally at one of five dose levels in the single dose phase, and one of four levels in the repeat dose phase. Each of the 28 enrolled subjects were sequentially assigned to a specific dose level and received two single-dose exposures at that same dose level (fasted and fed). The low dose cohorts were filled before assigning higher dose cohorts. The subjects were then assigned to receive one repeat-dose regimen. The lower dose repeat-dose cohorts are being filled before proceeding to higher repeat-dose levels. Dose levels are as follows:

- *single doses*: 650 mg (n = 6), 1,950 mg (n = 6), 2,925 mg (n = 6), 4,875 mg (n = 4), 6000 mg (n=6).
- *multiple dosing*: 650 mg TID (1,950 mg/day; n = 8), 975 mg TID (2,925 mg/day; n = 8), 1,625 mg TID (4,875 mg/day; n = 6), 2000 mg TID (6000 mg/day; n = 6).

Safety evaluations have not shown any significant drug-associated safety problems. Preliminary PK analyses show that the drug is absorbed with some variation in humans. Multi-day dosing has shown increased and sustained blood levels of free SA over a 24 hour cycle, consistent with expectations for an extended release formulation.

Phase 2 PK, PD and Safety (UX001-CL201): *"A Phase 2 Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Dose and Pharmacodynamic Efficacy of Sialic Acid-Extended Release (SA-ER) Tablets in Patients with GNE Myopathy or Hereditary Inclusion Body Myopathy".*

A Phase 2 randomized, placebo-controlled study has been performed to evaluate the safety and PD effects of SA-ER at two dose levels (3g and 6g/day). The study consists of a 24-week placebo-controlled Treatment Period, followed by an additional 24-week Treatment Continuation Period whereby all subjects receive active treatment. A planned analysis was conducted following completion of the 24-week placebo-controlled Treatment Period; the goal was to identify the dose that provides the best risk-benefit profile.

Results of planned PK, PD, clinical efficacy, and safety analyses following the 24-week placebo-controlled Treatment Period showed dose-dependent improvement in muscle strength relative to placebo, particularly in the upper extremities at the 6g SA-ER dose. These changes were statistically significant or trended towards significance, and were more pronounced in subjects that had greater walking ability at baseline, a predefined subset. Other clinical endpoints did not reveal changes at this Week 24 interim assessment. CK levels showed a trend to improvement in the 6g SA-ER dose group compared with placebo. SA-ER appeared to be well tolerated with no serious adverse events (SAEs) observed in either dose group. As expected, the highest dose (6g/day SA-ER) provided a sustained exposure, a clinical efficacy signal, and acceptable safety profile.

GNE Myopathy-Disease Monitoring Program: A natural history study collecting data on the disease characteristics and its progression is also in progress.

5.3 Summary of Overall Risks and Potential Benefits

Since SA is a normal body compound with native pathways for degradative metabolism and rapid renal clearance, there is no evidence or expectation of a significant safety issue with SA replacement therapy at this time. Data from nonclinical and clinical studies to date suggest SA-ER administered alone or with SA-IR does not pose any significant safety risks that can be identified at this time. Toxicology or adverse pharmacology findings were not observed in SA-treated animals; at very high doses, osmotic diarrhea may be observed in treated dogs. Interim safety results following a 24-week Treatment Period in a completed Phase 2 study (UX001-CL201), suggested an increase in diarrhea and GI symptoms relative to placebo. No correlation was observed between the GI events and free SA serum levels suggesting the frequency of GI events does not appear to be dose dependent.

In patients with GNE Myopathy, replacement of the substrate SA has the potential to restore normal sialylation of muscle glycoproteins and glycolipids, which could improve the function of muscle and limit the loss of muscle strength. It is not clear how much the effects of GNE Myopathy are reversible or if and how fast reversal of muscle disease might occur. The data in the HIBM mouse model suggest that over a one year period, substantial beneficial effects on the pathology of the disease are possible. However, it is not clear

whether advanced disease can improve, as opposed to preventing progression of existing disease. If the therapy has an effect comparable to that observed by Sparks and colleagues using intravenous immune globulin (IVIG) as a source of SA (Sparks et al. 2007), then the benefit to GNE Myopathy patients in improving muscle strength and function might be substantial. In clinical studies conducted to date, the highest dose (6g/day SA-ER) provided a sustained exposure, a clinical efficacy signal, and acceptable safety profile. Overall the risk-benefit ratio appears to be favorable based on the excellent safety record to date, and the potential benefit observed in nonclinical and clinical studies.

5.4 Study Rationale

GNE myopathy or HIBM is a severe progressive metabolic myopathy caused by a defect in the biosynthetic pathway for sialic acid (SA). Substrate replacement of SA is a potential therapeutic strategy based on evidence from relevant in vivo models, supported by PK characterization in a Phase 1 clinical study, and improvement in muscle strength from a Phase 2 randomized controlled trial. The first study showed some efficacy at the 6g dose level but not at 3g, indicating the dose level may be at the low end of the dose response curve. The interim data implied a clinical efficacy signal and acceptable safety profile suggesting the potential to optimize the therapeutic index by increasing SA exposure. Since successful use of SA replacement therapy in humans is believed to depend upon optimized exposure to the compound, an increased dose was suggested. Although administration of more extended release tablets could be utilized, data in canines suggests that administration of immediate release SA (SA-IR) in combination with the SA-ER will maximize absorption in the GI tract. Therefore a study testing an increased dose level combining SA-IR with SA-ER is proposed.

Subjects completing the 48-week UX001-CL201 study 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 is conducting this study in four 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 12g/day of SA (comprised of 1.5 g of SA-ER / 1.5 g of SA-IR treatment QID). Part III of the study reduces the dose from 12g/day to 6g/day for subjects who did not show additional benefit at 12g/day; however, treatment-naïve subjects and a small subset of rollover subjects will be invited to remain on the higher dose of 12g/day (described in Section 7.2). Part IV was added to change the formulation from SA-IR to SA-ER. The SA-IR dose formulation has been removed based on data showing that by the 4th day of dosing in a nonclinical study conducted in dogs, AUC for free SA was similar between the immediate and extended release formulations. In addition, a review of population data for Month 12 of Part III in the current study confirmed that 12g/day SA-IR did not appear to provide any additional benefit compared with 6g/day SA-ER, although some individual patients may have improved. Therefore, no further SA-IR will be administered after the initiation of Part IV; patients currently on 12g/day may continue receiving the 12g/day dose, if desired, by taking SA-ER.

6 STUDY OBJECTIVES

The safety objectives of the study are to:

- 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 (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 (Part II) over a 6 month treatment period
- Evaluate the safety of SA treatment at both 6g/day and 12 g/day (Part III [SA-ER/SA-IR] and Part IV [SA-ER]).

The clinical objectives of the study are to:

- Evaluate the long-term effect of SA treatment of GNE Myopathy subjects on muscle strength as measured by hand-held dynamometry (HHD)
- Evaluate the long-term effect of SA treatment of GNE Myopathy subjects on mobility, strength, and function using a series of physical performance measures
- Evaluate the long-term effect of SA treatment of GNE Myopathy subjects on functional disability using an interview-based questionnaire.

The exploratory objectives of the study are to:

- 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)
    - Determine whether a subset of subjects has additional benefit on the higher dose treatment.

7 INVESTIGATIONAL PLAN

7.1 Overall Study Design and Plan

This open-label extension study of will assess the long term safety and efficacy of SA 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.

Beginning with the Part II-Baseline Visit, all subjects currently enrolled in Part I will crossover to the SA-ER/SA-IR dosing regimen. Approximately 10 treatment naïve 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.

Part III of the study reduces the SA dose from 12g/day to 6g/day for subjects who did not show additional benefit at 12g/day at the interim analysis; however, treatment naïve subjects and a small subset of rollover subjects who showed a potential efficacy benefit will be invited to remain on the higher dose of 12g/day. Part III will assess the long-term safety and efficacy of 12g/day SA-ER/SA-IR treatment for the duration of the study for the subjects who stay on the higher dose in Part III and will provide additional information on the long-term safety and efficacy of 6g/day SA-ER for the remaining subjects.

Part IV was added to change the formulation from SA-IR to SA-ER. The SA-IR dose formulation has been removed based on data showing that by the 4th day of dosing in a nonclinical study conducted in dogs, AUC for free SA was similar between the immediate and extended release formulations. In addition, a review of population data for Month 12 of Part III in the current study confirmed that 12g/day SA-IR did not appear to provide any additional benefit compared with 6g/day SA-ER, although some individual patients may have improved. Therefore, no further SA-IR will be administered after the initiation of Part IV; patients currently on 12g/day may continue receiving the 12g/day dose, if desired, by taking SA-ER.

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 (Table 2.1 and Table 2.2). A Termination Visit will be conducted 4 weeks after subjects receive their last dose of study drug (last dose of study drug received at Month 36). For subjects who are eligible and choose to participate in the UX001-CL302 open-label extension study, the Month 36 Visit is considered the end of study visit and the Termination Visit is not required. Any subject who discontinues the current study early or is ineligible or decides not to participate in the UX001-CL302 extension study is required to have a Termination Visit 4 weeks after their last dose of study drug, as per Schedule of Events. Efficacy data analyses will be conducted at the end of the 36-month Treatment Period, although interim analyses may be performed 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.

7.2 Discussion of Study Design, Including Choice of Control Group

Part I of the study will focus on evaluating the long-term safety of 6g/day SA-ER treatment in GNE Myopathy subjects continuing SA-ER treatment as an extension of the 48-week, Phase 2 UX001-CL201 clinical study. Part I of the study will also explore long-term effects of SA-ER on clinical measures of muscle strength, mobility, function, disability and health-related quality of life. Exploratory evaluations of the effects of SA-ER on serum biomarkers will be performed in Part I of the study only.

Since Part I of the study is designed as an open-label extension designed to continue SA-ER treatment for subjects successfully completing the Phase 2 UX001-CL201 study, the study size and population are therefore restricted to said individuals. In UX001-CL201, safety and efficacy of SA-ER was examined in a randomized, double-blind study at two dose levels and compared to placebo treatment control. The current study design is not powered to assess statistically significant comparisons between treatment groups. Instead, the study population for Part I is intended to provide additional long-term safety data following maintenance treatment with 6g/day SA-ER. Since all subjects will receive the same treatment, randomization or blinding of study drug is not necessary.

The Week 24 interim data from the Phase 2 UX001-CL201 study implied a positive PD signal and acceptable safety profile suggesting the potential to optimize the therapeutic index by increasing SA exposure. Therefore, investigation into optimizing the risk-benefit profile of SA substrate replacement by examining higher SA doses is warranted. Part II of the study will assess the long-term safety and efficacy of an increased SA dose (total 12g/day) for up to 12 months. In this phase, SA treatment will be in the form of SA-ER tablets and immediate release capsules (SA-IR) to maximize absorption from the GI tract based on data obtained from nonclinical studies in canines. Continuing subjects will terminate Part I of the study

following approximately 12 weeks of treatment with 6g/day SA-ER and continue on to Part II of the study by crossing over to an increased daily SA dose of 12g/day. Since Part II of the study will be the first time GNE Myopathy subjects will be treated with the SA-ER/SA-IR investigational product, approximately 10 GNE Myopathy subjects will be enrolled to assess long-term safety and clinical efficacy of SA-ER/SA-IR in a treatment naïve population.

An interim analysis was conducted after 6 months of treatment with SA-ER/SA-IR; the results of this interim analysis have led to the establishment of Part III of the study. Part III will provide long-term safety and efficacy data on both 6 and 12g/day SA. This change is based on a review of individual subject data for the rollover subjects from the parent study UX001-CL201. The data analysis suggests that a small subset of subjects received an added benefit from the higher dose (defined as at least a 15% increase in either the UEC or LEC). The rollover subjects who met these criteria, along with the ongoing naïve subjects, had the option to remain on the 12g/day dose for the remainder of the study.

Part IV was added to change the formulation from SA-IR to SA-ER. The SA-IR dose formulation has been removed based on data showing that by the 4th day of dosing in a nonclinical study conducted in dogs, AUC for free SA was similar between the immediate and extended release formulations. In addition, a review of population data for Month 12 of Part III in the current study confirmed that 12g/day SA-IR did not appear to provide any additional benefit compared with 6g/day SA-ER, although some individual patients may have improved. Therefore, no further SA-IR will be administered after the initiation of Part IV; patients currently on 12g/day may continue receiving the 12g/day dose, if desired, by taking SA-ER.

Patients who elect to decrease from 12 g/day to 6 g/day may be allowed to do so upon Sponsor approval.

The 36-month treatment duration is intended to evaluate the long-term safety and efficacy of SA. While the lack of a control group may introduce difficulties in discerning natural disease progression from treatment effectiveness, due to the progressive debilitative nature of the disease, a placebo-controlled study of this duration is not feasible

7.3 Selection of Study Population

The study will be conducted in adult patients who have previously demonstrated mutations in the gene for the GNE/MNK enzyme leading to a diagnosis of GNE myopathy (variously termed HIBM, DMRV, or Nonaka disease). These patients are unable to synthesize endogenous SA, which leads to muscle weakness and atrophy. Consequently, this is the relevant population for testing SA replacement therapy to determine if exogenous SA leads to improved protein and lipid sialylation and stabilized or improved muscle structure and performance. The majority of the study population will consist of approximately 46 GNE Myopathy subjects who successfully completed UX001-CL201 and may or may not have

been previously exposed to SA-ER. Approximately 10 GNE Myopathy subjects who are SA and MaNAc-treatment naïve will be enrolled into Part II of the study.

The inclusion/exclusion criteria from the UX001-CL201 study inherently define the study population for subjects in Part I of the study, since successful completion of UX001-CL201 is requisite for enrollment in this study. The previous study was designed to allow for the enrollment of patients with a broad spectrum of physical disability, with at least 60% of enrolled subjects having residual lower extremity strength and function sufficient to walk ≥ 200 meters in the 6MWT. Enrolling patients across the spectrum of disease severity as subjects allowed the study to fully explore the safety and efficacy profile of SA-ER and inform the design of future studies. However, it should be noted that subjects unable to complete UX001-CL201 would not be eligible for this extension study, potentially introducing population bias toward subjects experiencing favorable safety and efficacy following up to 48 weeks treatment with SA-ER.

For the additional treatment naïve subjects enrolled into Part II of the study, the diagnosis and age range are the same as requirements for continuing subjects. This subgroup will be restricted to GNE Myopathy subjects with the ability to walk at least 200 meters during the 6MWT. Since the strongest clinical efficacy signal was observed in this subset of GNE Myopathy subjects participating in the UX001-CL201 study, this protocol was designed to enroll those subjects most likely to obtain clinical benefit from study treatment.

7.3.1 Inclusion Criteria

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

- Enrollment in and successful completion of the UX001-CL201 protocol **OR** (for 10 treatment naïve subjects):
  - Have a confirmed diagnosis of GNE Myopathy
  - Aged 18 -65 years of age, inclusive
  - Able to walk ≥ 200 meters and < 80% of predicted normal during the 6MWT (orthotics and assistive devices allowed)
  - No prior history of treatment with SA or MaNAc
- Must be willing and able to provide written, signed informed consent after the nature of the study has been explained, and prior to any research-related procedures
- Must be willing and able to comply with all study procedures
- Sexually active subjects must be willing to use an acceptable method of contraception while participating in the study
- Females of childbearing potential must have a negative pregnancy test at Baseline and be willing to have additional pregnancy tests during the study. Females considered not of childbearing potential include those who have been in menopause for at least two years,

or have had tubal ligation at least one year prior to Baseline, or who have had total hysterectomy.

7.3.2 Exclusion Criteria

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

- Pregnant or breastfeeding at Baseline or planning to become pregnant (self or partner) at any time during the study
- Use of any investigational product (other than SA-ER tablets) to treat GNE Myopathy
- Ingestion of ManNAc or similar SA producing compounds
- Has had any hypersensitivity to SA or its excipients that, in the judgment of the investigator, places the subject at increased risk for adverse effects
- Have any co-morbid conditions, including unstable major organ-system disease(s) that in the opinion of the Investigator, places the subject at increased risk of complications, interferes with study participation or compliance, or confounds study objectives.

7.3.3 Removal of Subjects from Therapy or Assessment

In accordance with the Declaration of Helsinki, subjects have the right to withdraw from the study at any time for any reason. The principal investigators and Ultragenyx also have the right to remove subjects from the study. Subjects may be removed from the study for the following reasons:

- Occurrence of an unacceptable AE
- An illness that, in the judgment of the principal investigator or Ultragenyx, might invalidate the study or place the subject at risk
- At the request of the subject, principal investigator, or Ultragenyx, whether for administrative or other reasons
- Protocol deviation or unreliable behavior

If the reason for removal of a subject from the study is an AE, the AE and any related test or procedure results will be recorded in the source documents and transcribed onto the Case Report Form (CRF). Each clinically significant abnormal laboratory value or other clinically meaningful abnormality should be followed until the abnormality resolves or until a decision is made that it is not likely to resolve. If such abnormalities do not return to normal within 30 days after the last dose given, their etiology should be identified and Ultragenyx should be notified. All unscheduled tests must be reported to Ultragenyx immediately.

If a subject discontinues from the study prematurely, every reasonable effort should be made to perform the (Early) Termination Visit procedures within four weeks of discontinuation.

Subjects who withdraw or are removed from the study after receiving study drug may not re-enter the study.

7.3.3.1 Stopping Rules

A DMC will be constituted for Study UX001-CL202 and will act in an advisory capacity to Ultragenyx to monitor the safety of SA-ER/SA-IR in subjects who participate in the study (see Section 7.6.3). The DMC may provide advice to Ultragenyx in any determination of whether study enrollment should be paused or if the study should be halted.

AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE). If two subjects develop the same unexpected Grade 3 AE that is possibly or probably related to study drug or any subject develops an unexpected Grade 4 AE that is possibly or probably related to study drug, enrollment of new subjects may be suspended until a thorough evaluation can be performed. Should these AEs occur, a full clinical evaluation will be performed by the medical monitor, principal investigators, and DMC in order to make a decision regarding what actions to take, including whether to suspend or resume enrollment, or recommend stopping the study after Institutional Review Board (IRB)/Ethics Committee (EC) review. The recommendations from the medical monitor and investigators will be forwarded to the IRB/EC for review and approval.

7.4 Treatments

7.4.1 Treatments Administered

The SA-ER investigational product will consist of tablets containing 500 mg of SA active ingredient in an extended release formulation. In Part I of the study, the 6000 mg (6g) total daily SA-ER dose will be self-administered by the oral route and will be divided into a three TID regimen; all subjects will self-administer four 500 mg tablets in the morning, four tablets in the early evening, and four SA-ER tablets qHS.

The SA-IR investigational product will consist of capsules containing 500 mg of SA active ingredient in an immediate release formulation. In Part II of the study, the 12,000 mg (12g) total daily SA dose will be self-administered by the oral route and will be divided into a QID regimen; all subjects will self-administer three 500 mg tablets (1.5g SA-ER) and three 500 mg capsules (1.5g SA-IR) in the morning, afternoon, early evening, and qHS.

In Part III of the study, for those subjects on the 12g/day dose, each dose of SA-ER/SA-IR will consist of SA-ER tablets, each containing 500 mg of SA active ingredient in an extended release formulation and SA-IR capsules, each containing 500 mg of SA active ingredient. During the Treatment Period, the 12,000 mg (12g) total daily SA dose will be administered by the oral route and will be divided into a TID or QID regimen. If tolerability issues arise, the dose may be temporarily stepped down until symptoms resolve.

In Part III of the study, for those subjects on the 6g/day dose, each dose of SA-ER will consists of tablets, each containing 500 mg of SA active ingredient in an extended release

formulation. During the Treatment Period, the 6000 mg (6g) total daily SA-ER dose will be administered by the oral route and will be divided into a TID regimen.

Part IV: 6g/day dose and 12g/day dose – Each dose of SA-ER will consists of tablets, each containing 500 mg of SA active ingredient in an extended release formulation. During the Treatment Period, the 6g total daily SA-ER dose will be administered by the oral route and will be divided into a TID regimen. The 12g total daily SA-ER dose will be administered by the oral route and will be divided into a TID or QID regimen.

Subjects will be instructed to take all study medication with food in the morning, the afternoon, early evening, and/or qHS (i.e. within 30 minutes following a meal or snack).

7.4.2 Identity of Study Drugs

The study drugs for protocol UX001-CL202 are white, oval, SA-ER tablets and naturally colored, size 000, hard gelatin SA-IR capsules for oral administration. No animal-derived products are used in the manufacture of the tablets. Where bovine gelatin is used for production of gelatin capsules, it is in compliance with pharmaceutical regulatory statutes. The study drugs were manufactured, packaged, and labeled according to Good Manufacturing Practice (GMP) regulations.

Study drug tablets will be packaged in bottles. Each bottle will contain 168 tablets or capsules, equivalent to 2 weeks of study drug supply. During Part I, subjects will receive an approximate 6 week supply at the Baseline and Week 6 visits. For Week 6 and Week 12 visits, the visit window is ± 0 days. For the duration of the study, subjects will be instructed to return all unused study drug to the next visit.

Study drug will be dispensed at in-clinic visit. Additional drug may be shipped to subjects by the investigative site in between scheduled clinic visits.

Bottles will be labeled with the study number (UX001-CL202). The bottle will display the protocol number (UX001-CL202), the name and city, state, and zip code of the study sponsor (Ultragenyx Pharmaceutical Inc.), the storage conditions, expiration date, and the statement "Caution: New Drug – Limited by Federal (US) Law to Investigational Use".

7.4.2.1 Investigational Product

SA-ER 500 mg tablets are white to off-white, extended release, oval tablets intended for oral administration. The tablet formulation contains approximately 43.3% active pharmaceutical ingredient in a mixed polymer matrix developed for extended release of SA over 24 hours. Tablets are manufactured by a formulation process using wet aqueous granulation; the blend is then dried and compressed into tablets. SA-ER 500 mg tablets are 1150 mg in total weight.

SA-IR 500mg capsules are naturally colored, size 000, immediate release, hard gelatin capsules designed for oral administration. The capsule formulation contains approximately

93.5% active pharmaceutical ingredient. Manufacturing consists of dry blending followed by filling into capsules. SA-IR capsules have a fill weight of approximately 535 mg and a total weight of approximately 698 mg.

7.4.3 Selection of Doses and Study Duration

***Part I - SA-ER Treatment Period*:** In Part I of this Phase 2 open label extension study, SA-ER will be administered orally TID for a total dose of 6000 mg/day (6g SA-ER). The SA-ER dose and regimen for Study UX001-CL202 was selected based on the following information:

- Analyses of SA PK in the Phase 1 study UX001-CL101 indicate that orally administered doses of SA-ER at 2000 - 6000 mg/day divided into TID dosing is effectively absorbed in humans, and multiple day dosing at doses up to 6000 mg/day achieves steady, increased levels of free SA in the serum with some individual variation.
- In the Phase 1 study, single oral doses of SA-ER at up to 6g SA-ER and seven days of treatment at up to 6g/day have been administered without any significant drug-associated safety problems.
- Malicdan and colleagues have demonstrated that 20 mg/kg/day SA given orally as replacement therapy effectively prevented disease in a mouse model of HIBM (Malicdan et al. 2009). Using the allometric scaling method suggested by the US FDA (FDA Guidance for Industry 2005), the human equivalent dose is 12.5 times higher; a mouse dose of 20 mg/kg/day is equivalent to a human dose of 1.6 mg/kg/day.
- Toxicology studies have identified the NOAEL to be 2000 mg/kg in dogs and rats, far above the proposed human dose level of 6g/day SA-ER in Part I of the study.
- TID dosing in conjunction with an extended release formulation is able to achieve steady increased levels of SA over the 24 hour cycle.
- To date, no SAEs have been observed from an ongoing Phase 2 randomized, placebo-controlled study evaluating the safety and PD effects of 3g/day and 6g/day SA-ER.

Based on these data, the 6g/day total daily dose selected for Part I of the Phase 2 extension study is deemed reasonable. The use of doses above that tested in preclinical mouse models accounts for species-specific differences in absorption and/or biological activity. Based on Phase 1 clinical data, steady state SA levels are achieved with TID dosing: in the morning, early evening, and qHS. The qHS dose is particularly important to assure coverage during the night.

***Part II - SA-ER/SA-IR Treatment Period*:** Successful use of SA replacement therapy in humans is believed to depend upon optimized exposure to the compound. Interim results from the UX001-CL201 study suggest an increased dose of therapy is warranted. In Part II of this Phase 2 open label extension study, 12g SA will be administered orally via 1.5g of

SA-ER tablets and 1.5g SA-IR capsules, QID. The SA-ER/SA-IR dose and regimen for Study UX001-CL202 was selected based on the following additional information:

- **Dose effect at 6g only.** Interim results from UX001-CL201 suggest the 6g SA-ER dose level appears to be at the lower end of the effective range since a clinical efficacy signal was observed but 3g SA-ER had almost no effect.
- **The SA level correlates with treatment effect based on HHD.** The Week 24 interim data imply a positive PD signal and acceptable safety profile suggesting the potential to optimize the therapeutic index by increasing SA exposure.
- **Canine studies show that immediate release most effective way to increase SA.** Studies in normal canines showed that more than proportional increases in absorption of SA are possible if an immediate release formulation was mixed with an extended release formulation. The concept is that the immediate release product enhances stomach absorption which is not well utilized by extended release formulated tablets.
- **QID therapy should support higher SA levels.** Since SA-IR is rapidly cleared, a QID dosing regimen is predicted to provide optimized continuous exposure to SA. Administration of a 12g total daily dose of SA would therefore be divided into 4 equal doses of 3g each (1.5g SA-ER + 1.5g SA-IR), representing only a 50% increase for each dose.
- **Safety of very high SA doses.** In a chronic toxicology study in rats, the NOAEL was 2000 mg/kg SA, which is provides a safety margin of approximately 1.4-fold for the proposed 12g/day dose level. In a 6 month oral toxicity study in dogs, the NOAEL was 2000 mg/kg SA, which provides a safety margin of approximately 5-fold for the human 12g/day dose level.
- **Single doses of 6g SA-ER given in one dose were well tolerated**. In the Phase 1 PK and tolerability study, 6g SA-ER was administered to GNE Myopathy subjects in a single oral dose and was well tolerated with no SAEs observed.

Based on these data, the 12g/day total daily dose selected for Part II of the Phase 2 extension study is deemed reasonable. Results of nonclinical studies in canines suggest the administration of SA in extended-release and immediate-release form can improve overall absorption of SA-ER and increase free SA levels in the serum. Although administration of more extended release tablets could be utilized, data in canines suggests that administration of SA-ER/SA-IR will maximize absorption in the GI tract.

***Part III – 12g/day SA-ER/SA-IR or 6g/day SA-ER Treatment Period*:** This change is based on a review of individual subject data for the rollover subjects from the parent study UX001-CL201. The data analysis suggests that a small subset of subjects received an added benefit from the higher dose. The rollover subjects who meet these criteria, along with the ongoing naïve subjects, will have the option to remain on the 12g/day dose for the remainder of the study.

Part IV – 12g/day SA-ER or 6g/day SA-ER Treatment Period: Part IV was added to change the formulation from SA-IR to SA-ER. The SA-IR dose formulation has been removed based on data showing that by the 4th day of dosing in a nonclinical study conducted in dogs, AUC for free SA was similar between the immediate and extended release formulations.
In addition, a review of population data for Month 12 of Part III in the current study confirmed that 12g/day SA-IR did not appear to provide any additional benefit compared with 6g/day SA-ER, although some individual patients may have improved. Therefore, no further SA-IR will be administered after the initiation of Part IV; patients currently on 12g/day may continue receiving the 12g/day dose, if desired, by taking SA-ER.

Study Duration: The maximum treatment duration for Part I of the study will be 12 weeks to allow crossover to Part II of the study. The Parts II, III, and IV treatment durations of approximately 36 months enables a long-term assessment of the safety and efficacy of SA-ER/SA-IR and SA-ER in subjects with GNE Myopathy.

7.4.4 Prior and Concomitant Therapy

7.4.4.1 Prohibited Medications

Patients may not be enrolled if they have used any investigational product (other than SA-ER tablets) or investigational medical device prior to Baseline, or if they require any investigational agent prior to completion of all scheduled study assessments. Ingestion of ManNAc, SA, or related metabolites; IVIG; or anything that can be metabolized to produce SA in the body is prohibited during the 60 days prior to Baseline and throughout the study. If ManNAc, SA or other substrate was used more than 60 days prior to Baseline, the time period of use, the compound used, and the dose and dose regimen should be recorded in the subject's history. If a patient has been on substrate replacement therapy in the past, the investigator must consider the potential confounding effects of this therapy before enrolling the patient as a subject in the study.

IT IS ESSENTIAL THAT THE SUBJECT COMMIT TO NOT INGESTING ManNAc OR SIMILAR OTHER SA-PRODUCING COMPOUNDS DURING THE CONDUCT OF THIS STUDY AS IT COULD CONFOUND THE INTERPRETATION OF RESULTS.

7.4.4.2 Permitted Medications

Other than the medications specifically prohibited in this document, subjects may receive concomitant medications as required. Medications (investigational, prescription, over-the-counter, and herbal) and nutritional supplements taken during the 60 days prior to Baseline will be reviewed and recorded. At the Baseline visit, current medications will be recorded. If a subject takes any medication other than SA-ER during study treatment, the subject should record the date and time the medication was taken, the name of the medication, and the reason the medication was taken in the drug administration diary; this data will be recorded in the subject's CRF.

Any non-study therapies received during study participation will be similarly recorded in the subject's medical record and CRF.

7.4.5 Treatment Compliance

Subjects will be asked to maintain a record of self-administration in a drug accountability diary; the diary will be reviewed at each study visit. Subjects will be instructed to return all unused study drug to the next visit. Drug accountability diaries will be collected by site personnel at the clinic visits. Site personnel will maintain a record of all medication dispensed to each subject and all unused medication returned to the site. In Parts II, III, and IV of the study, site personnel will make periodic calls to subjects to ensure treatment compliance.

7.5 Study Procedures and Assessments

7.5.1 Schedule of Events

The Part I 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 study. Following the signing of informed consent at the Part I Baseline visit, each subject will be dispensed study drug and will return for assessments according to the Part I Schedule of Events (Table 2.1).

For subjects continuing treatment during Part I, the Part II Baseline Visit will be conducted in conjunction with the Part I Termination Visit. Additional treatment-naïve subjects will be enrolled directly into Part II of the study, with screening and baseline assessments taking place at the Part II Baseline Visit. Following the signing of informed consent at the Part II Baseline visit, each subject will be dispensed study drug and will return for assessments according to the Schedule of Events (Table 2.2).

The Termination Visit occurs four weeks after subjects receive their last dose of the study (last dose of study drug received at Month 36). The Termination Visit is not required for subjects who are eligible and choose to participate in the extension study, but must be completed for any subject who terminates study participation early or decides not to participate in the UX001-CL302 open-label extension study. 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.

The parameters to be assessed in Study UX001-CL202, along with timing of assessments for each part of the study, are provided in the Schedule of Events (Table 2.1 and Table 2.2).

7.5.2 Clinical Efficacy Measures

The clinical efficacy measures in this study will evaluate muscle strength, mobility and function using the evaluations detailed below. Assessments will be conducted as indicated in the Schedule of Events (Table 2.1 and Table 2.2, respectively). Portions of the tests may be videotaped to monitor test administration and assess for qualitative changes in function (e.g., gait). Subject identity will be protected by blurring the facial area in the video(s). Refer to the Clinical Evaluator Manual for additional details on clinical efficacy measures.

7.5.2.1 Hand-held dynamometry

In Part I of the study, HHD testing will be performed at the Baseline and Part I Termination Visits, to assess muscle strength. For continuing subjects, the assessment at the Part I Termination Visit will serve as the baseline assessment for Part II of the study. HHD testing in Parts II, III, and IV of the study will be performed at Baseline (for treatment naïve subjects), Months 3, 6, 12, 18, 24, 30, 36 and Termination Visits. Formal training will be conducted with the licensed physical therapists administering the HHD testing to standardize technique and minimize variability. The maximum voluntary isometric contraction (MVIC) against a dynamometer will be used to measure strength in the following muscle groups: shoulder abductors, elbow flexors, elbow extensors, hip abductors, hip adductors, hip flexors, hip extensors, knee flexors and knee extensors. A hand dynamometer will be used to assess gross grip strength and a pinch dynamometer will be used to assess pinch strength.
Each effort will last approximately three seconds with a slow build to a maximum voluntary force. Strength in the elbow flexors and elbow extensors will be measured with the subject lying in a supine position on an examination table. Strength in the hip extensors will be measured with the subject leaning over an examination table in a prone position. All other muscle groups will be tested with the subject in a sitting position. All measurements will be taken bilaterally. The administrator will attempt to obtain two force values within approximately 15% of each other for each muscle group. Testing positions may be altered at the discretion of the administrator to improve the reliability of the test. The total force (in kg) will be recorded at the time of test administration. The highest force value collected for each muscle group will be used for data analysis. The percent of predicted normal values will be calculated after the testing using published normative data (Mathiowetz et al. 1985); (NIMS 1996); (Bohannon 1997b); (Bohannon et al. 2006); (Peters et al. 2011).

7.5.2.2 Six Minute Walk Test

In Part I of the study, the 6MWT (Solway et al. 2001) will be administered at Baseline and the Part I Termination Visits to assess walking ability. For continuing subjects, the assessment at the Part I Termination Visit will serve as the baseline assessment for Part II of the study. In Parts II, III, and IV of the study, the 6MWT will be administered at Baseline (for treatment naïve subjects), Months 3, 6, 12, 18, 24, 30, 36 and Termination Visits.
The 6MWT will be administered by a licensed physical therapist in accordance with American Thoracic Society (ATS) guidelines (ATS 2002). Blood pressure, heart rate and self-reported Borg scale dyspnea and fatigue ratings will be recorded before and after the test

administration. ATS guidelines require a subject to have a pre-test resting heart rate of less than 120 beats/minute, systolic blood pressure of less than 180 mm Hg and diastolic blood pressure of less than 100 mm Hg to ensure safety. Subjects who meet the safety criteria will be instructed to walk the length of a pre-measured 20 meter course for six consecutive minutes. Traffic cones will be used to standardize the distance in hallways longer than 20 meters. The subject will walk laps around the cones until the six minute time period has expired. However, the test will not be interrupted and the subject will continue to walk for the 6-minute duration of the test. Instructions and encouragement will be given according to the script provided in the ATS guidelines. The distance walked at the end of six minutes will be recorded in meters at the time of test administration. The percent of predicted normal values will be calculated after the testing using published normative data (Gibbons et al. 2001).

7.5.2.3 Walking Speed Test

In Part I of the study, the walking speed test will be administered at Baseline and the Part I Termination Visits to assess gait speed. In Parts II, III, and IV of the study, the walking speed test will be administered at Baseline (for treatment naïve subjects), Months 3, 6, 12, 18, 24, 30, 36 and Termination Visits. The test will be administered twice by a licensed physical therapist, once at a comfortable speed and once at a maximum speed. Subjects will be instructed to walk the length of a pre-measured 25 foot (7.62 meter) course. Traffic cones or tape on the floor will be used to standardize the distance. Subjects will have a few feet at the beginning and the end of the 25 foot course to allow for acceleration and deceleration. For the comfortable speed test, subjects will be instructed to walk at their normal pace. For the maximum speed test, subjects will be instructed to walk as fast as they safely can without running. The total number of seconds required to complete the test for each speed will be recorded in seconds at the time of test administration. Subject performance relative to peers will be calculated after the testing using published normative data (Bohannon 1997a).

7.5.2.4 Weighted Arm Lift Test

In Part I of the study, the weighted arm lift test (Agarwal et al. 2006) will be administered at Baseline and the Part I Termination Visits, to assess upper limb function. In Parts II, III, and IV of the study, the weighted arm lift test will be administered at Baseline (for treatment naïve subjects), Months 3, 6, 12, 18, 24, 30, 36 and Termination Visits. The test will be administered by a licensed physical therapist. The subject will be asked to sit in a chair holding a 1 kg barbell with the shoulder adducted, the elbow in full flexion and the forearm in supination. On command, the subject will be asked to lift the arm above the head until the elbow is fully extended, then to lower the arm back to the starting position. The subject will be asked to repeat the action at a comfortable pace according to their own rhythm for the 30 second duration of the test. The test will be performed bilaterally and the final score will be the mean of the total number of completed repetitions from both arms. The number of completed repetitions from each arm and the mean score will be recorded at the time of test administration.

7.5.2.5 HIBM Functional Activities Scale

In Part I of the study, the HIBM Functional Activities Scale (HIBM-FAS) will be administered at the Baseline and Part I Termination Visits, to assess functional disability. For continuing subjects, the assessment at the Part I Termination Visit will serve as the baseline assessment for Part II of the study. Additional HIBM-FAS assessments in Parts II, III, and IV of the study will be performed at Baseline (for treatment naïve subjects), Months 6, 18, 36 and Termination Visits. The scale is being developed specifically for patients with GNE myopathy (HIBM) based on feedback received from affected individuals on the impact of the disease on their function. Items in the scale assess the subject's ability to independently perform various activities of living that involve self-care, mobility and use of the upper and lower extremities. The scale will be administered in an interview format by a licensed physical therapist and scored after the testing.

7.5.3 Exploratory Efficacy Measures

Additional novel exploratory biomarkers of sialylation and muscle injury may also be evaluated to explore the possible best methodology to monitor GNE Myopathy disease. Candidate biomarkers present in serum may include:

- CK levels
- Neural cell adhesion molecule (NCAM) measured using an ELISA assay and/or immunoblot assay to characterize the NCAM types present.
- Other biomarkers of muscle injury and remodeling, including MMP9 and microRNAs

Assessment of serum protein markers will only be conducted in Part I of the study. In Parts II, III, and IV of the study, CK levels will be the only exploratory efficacy measure assessed.

7.5.4 Safety Measures & General Assessments

7.5.4.1 Medical History

For continuing subjects, the medical history information obtained during the UX001-CL201 study will carry over to this study. A detailed medical history, including a GNE Myopathy-specific medical history, will be obtained at Screening/Baseline Visit for new subjects entering the study (i.e. treatment naïve individuals). The medical history will solicit information on any prior or existing medical conditions that might interfere with study participation or safety. This medical history should elicit all major illnesses, diagnoses, and surgeries to date.

7.5.4.2 Interval History

Each interval history is intended to record any signs, symptoms, or events (e.g., falls) experienced by the subject since the prior study visit that are not related to study procedure(s) performed at prior study visits or study drug. Interval history may include exacerbation or

improvement in existing medical conditions (including the clinical manifestations of GNE Myopathy) that might interfere with study participation, safety, and/or positively or negatively impact performance of functional assessments. Interval history may identify under-reported AEs, and will be collected at the study visits indicated in the Schedule of Events (Table 2.1 and Table 2.2).

7.5.4.3 Vital Signs

Vital signs will include seated systolic blood pressure and diastolic blood pressure measured in millimeters of mercury (mm Hg), heart rate in beats per minute, respiration rate in breaths per minute, and temperature in degrees Celsius (°C). Vital signs measurements will be performed at study visits indicated in the Schedule of Events (Table 2.1 and Table 2.2).

7.5.4.4 Height and Weight Evaluations

Measurements of height and weight will be collected on each subject using a stadiometer and a scale by the physical therapist administering the performance testing. Height and weight data will be used to evaluate each subject's muscle strength and function using published normative data where available.

7.5.4.5 Physical Examination

In Part I of the study, complete physical examinations will be performed at the Baseline and Part I Termination Visits. For continuing subjects, findings in the Part I Termination Visit will serve as the Part II baseline assessment. In Parts II, III, and IV of the study, a complete physical examination will be performed at Baseline (for treatment naïve subjects), Months 6, 18, 36 and the Termination Visits. Physical examinations will include assessments of general appearance; head, eyes, ears, nose, and throat; the cardiovascular, dermatologic, lymphatic, respiratory, gastrointestinal, genitourinary, musculoskeletal, neurologic systems (at designated visits where a complete neurological examination is not performed). Other body systems may be examined and symptoms of increasing muscle weakness and pain will be recorded. The presence of changes in muscle pain or weakness should be evaluated carefully by a complete neurologic exam when these changes are reported by subjects. The specific muscle location and pain should be noted. Clinically significant changes from Baseline will be recorded as AEs.

7.5.4.6 Neurological Examination

In Part I of the study, a neurological examination will be performed at the Baseline and Part I Termination Visits. For continuing subjects, findings in the Part I Termination Visit will serve as the Part II baseline assessment. In Parts II, III, and IV of the study, a neurological examinations will be performed at Baseline (for treatment naïve subjects), Months 6, 18, 36 and the Termination Visits. The neurological examination will include assessments of cognition, cranial nerves, motor function, coordination and gait, reflexes, and sensory function.

7.5.4.7 Clinical Laboratory Tests

The clinical laboratory evaluations to be performed in this study are listed in Table 7.5.4.7.1; the time points for these evaluations are indicated in the Schedule of Events (Table 2.1 and Table 2.2). Fasting is not required. Refer to the central laboratory manual for additional details.

Table 7.5.4.7.1: Clinical Laboratory Assessments

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

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

7.5.4.8 Adverse Events

All AEs will be recorded from the time the subject signs the informed consent until 30 days after the last dose of study drug or, if applicable, until the date the subject signs the informed consent for the open-label extension study, UX001-CL302, whichever occurs sooner. The determination, evaluation, reporting, and follow-up of AEs will be performed as outlined in Section 8.5. At each visit subjects will be asked about any new or ongoing AEs since the previous visit. Assessments of AEs will occur at every study visit.

7.5.4.9 Concomitant Medications

Concomitant medications will be reviewed and recorded at each study visit. A discussion of concomitant medications is provided in Section 7.4.4.

7.5.4.10 Pregnancy Testing

Female subjects of childbearing potential will have urine pregnancy tests as specified in the Schedule of Events (Table 2.1 and Table 2.2). Female patients with a positive pregnancy test at Baseline do not meet eligibility criteria for enrollment and will not be enrolled in the study. Females considered not of childbearing potential include those who have had total hysterectomy, have been in menopause for at least two years, or have had tubal ligation at least one year prior to Baseline.

Additional pregnancy tests will be performed at any visit in which pregnancy status is in question. A serum pregnancy test will be performed in the event of a positive or equivocal urine pregnancy test result.

Experience with UX001 in pregnant women is limited. The study drug may involve risks to a pregnant female or unborn baby which are currently unknown. Participants of child-bearing potential or with partners of child bearing potential who have not undergone a bilateral salpingo-oophorectomy and are sexually active must consent to use a highly effective method of contraception as determined by the site investigator from the period following the signing of the informed consent through 30 days after last dose of study drug. Examples of highly effective methods of contraception include oral hormonal contraceptives, patch hormonal contraceptives, vaginal ring, intrauterine device, physical double-barrier methods, surgical hysterectomy, vasectomy, tubal ligation or true abstinence (when this is in line with the preferred and usual lifestyle of the subject), which means not having sex for the duration specified above because the subject chooses not to.

7.5.4.11 Pregnancy in Subject or Partner

Pregnancies in subjects or partners must be reported within 24 hours of knowledge of the event to Ultragenyx or its designee. The investigator must make every effort to follow the pregnancy of either subject or partner through resolution of the pregnancy (delivery or termination) and report the resolution to Ultragenyx or its designee. In the event of a pregnancy in the partner of a subject, the investigator should make every effort to obtain the

female partner's consent for release of protected health information. Refer to the Study Reference Manual for details on the reporting procedures to follow in the event of pregnancy.

7.5.5 Drug Concentration Measurements

Blood samples for the measurement of trough levels of free serum SA will be drawn at the time points shown in the Schedule of Events (Table 2.1 and Table 2.2); samples will be obtained from the subjects during blood draws for clinical laboratory samples.
Urine samples for measurement of free serum SA will be collected during Part I of the study only. The time elapsed from the last dose of study drug should be noted. SA, the active study drug in UX001-CL202, occurs naturally in the human body, both through de novo synthesis and via the diet. Consequently, the free serum SA level should reflect, but will not be a quantitative measure, of circulating study drug. Refer to the central laboratory manual for details on the drug concentration measurements.

7.5.6 Appropriateness of Measures

The efficacy parameters to be evaluated in this study include clinical changes in muscle strength, and subject mobility, and function. The clinical assessments in the study employ standard performance measures used in other neuromuscular diseases and conditions that cause muscle weakness and impaired function. Based on the work of Aitkens (Aitkens et al. 1989), the study will focus on quantitative muscle testing. The strength of a set of muscle groups in the upper and lower extremities will be assessed by HHD, a form of quantitative muscle testing that uses a device with a strain gauge to measure force during a MVIC (Sisto et al. 2007) . Walking ability will be assessed using the 6MWT test, a commonly used test of endurance used in clinical trials for various indications that has served as the basis for many product approvals. In addition, an interview-based measure designed to evaluate disability in GNE Myopathy patients (HIBM-FAS) will be administered in this study to further validate the instrument.

Exploratory measures will attempt to identify changes in serum biomarkers in Part I of the study. Serum NCAM may be evaluated to provide some estimate of the sialylation of NCAM in the regenerating muscle, albeit at low levels in the circulation. Other biomarkers of muscle injury (e.g., MMP9 and microRNAs) may also be assessed. However, interim data from the UX001-CL201 study suggests the results may be of limited value; therefore, exploratory serum protein markers will not be assessed in Parts II, III, and IV of the study.

Serum CK level will be assessed as a measure of muscle injury throughout the study; a positive dose-dependent decrease in serum CK levels was observed in the UX001-CL201 Week 24 analysis. Unlike other myopathies, CK activities are mildly elevated or in the normal range for these patients; 22/58 patients reported by three publications had two-times or higher elevations (Sadeh et al. 1993); (Mizusawa et al. 1987); (Sunohara et al. 1989). The mouse model of HIBM showed elevated CK levels that improved substantially on treatment (Malicdan et al. 2009). Given the modest CK levels in patients, it is unclear if this

is a universally evaluable endpoint in humans, however in the mouse model, the data on reduced CK levels during SA treatment was compelling (Malicdan et al. 2009).

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

7.6 Statistical Methods and Determination of Sample Size

Because the completeness of the data affects the integrity and accuracy of the final study analysis, every effort will be made to ensure complete, accurate and timely data collection, and to avoid missing data. In particular the endurance measures will be performed in duplicate using standard and consistent methodology. The detailed method for analyses will be presented in the Statistical Analysis Plan (SAP); the information below is intended as a guide to planned analyses.

7.6.1 Clinical and Exploratory Efficacy Measures

The clinical evaluation measures in this study are:

- Improvement in quantitative muscle strength as measured by HHD.
- Improvement in mobility, strength and gross motor function as measured by the 6MWT and walking speed and weighted arm lift tests.
- Improvement in functional disability as measured by the HIBM-FAS.

The exploratory efficacy measures in this study will involve evaluation of novel biomarkers of sialylation and muscle injury. The exploratory efficacy measures may include:

- Improvement in serum biomarkers of muscle injury, including CK.
- Improvement in other serum biomarkers of muscle injury, sialylation, and remodeling, including MMP9 (metalloproteinase level) and specific microRNAs associated with muscle disease.

Serum biomarkers of sialylation will be evaluated as exploratory analyses in Part I of the study only. Serum CK levels will be evaluated in Parts I, II, III, and IV of the study.

7.6.1.1 Clinical Efficacy Analyses

All subjects with any post-dose data will be included in the intent-to-treat (ITT) efficacy analysis.

Efficacy will be evaluated by continued improvement in clinical assessments. Efficacy assessments may differ depending on the phase of the study (i.e., Part I, Part II, Part III, or

Part IV). For Part I efficacy evaluation, results from the last pre-treatment assessment from UX001-CL201 will be compared with the last post-treatment assessment for the Part I Treatment Period as listed in the Schedule of Events (Table 2.1), with efficacy conclusions based on change since SA-ER treatment initiation. An interim analysis will be conducted when a majority of subjects have completed the Month 6 Visit of the Part II Treatment Period. For Part II efficacy evaluation of the continuing subjects, change from baseline of Part II to Month 6 assessment at 12g/day SA-ER/SA-IR dose will be determined and compared with the improvement observed during the first 6 months of treatment with 6 g/day SA-ER dose, and to the rate of change observed with placebo or 3g treatment during the first 6 months of the study.

The changes from baseline of the treatment-naïve subjects will be evaluated over time. Potential comparisons of the changes from baseline to Month 6 will be performed for the 6MWT, UE, and LE between the naïve group versus the placebo and 6g/day treatment groups for the first 24 weeks of treatments in subjects able to walk more than 200m at baseline. In addition, changes in muscle strength over the entire treatment period of subjects who started with 6g/day and 3g/day will be evaluated and compared to the projected values of subjects who received placebo for the first 24 weeks of treatment in UX001-CL201.

A full accounting of the analyses for Parts III and IV of the study will be provided in the Statistical Analysis Plan.

For those clinical evaluations with repeated assessments (i.e., HHD, 6 MWT, walking speed and weighted arm lift tests) the analysis will be performed using a repeated measures analysis. An exchangeable variance-covariance structure will be used. The final treatment effect estimate based on this model will be the estimated treatment difference at Month 36. The purpose of including data from assessments prior to Month 36 is to increase the precision of the estimated variance, while using categorical effects of time-by-treatment to avoid modeling assumptions.

Muscle strength as measured by HHD will be reported as force in kg and percent of predicted normal force based on age, gender, height and weight (where applicable). Changes in force and percent of predicted normal force will be assessed for gross grip, pinch, shoulder abductors, elbow flexors, elbow extensors, hip abductors, hip adductors, hip flexors, hip extensors, knee flexors, and knee extensors. Individual muscle groups will also be compared to assess individual muscle changes.

Walking ability as measured by the 6MWT will be reported as distance in meters and percent of predicted normal based on age and gender. Changes in distance and percent of predicted normal will be assessed. The proportion of subjects with a normal percent predicted distance walked (i.e., a percent predicted distance walked of $\geq 80\%$) at each time point may be tabulated. The relationship between 6MWT results and other and efficacy outcomes may also be explored.

Walking speed as measured by the 25 feet walk test will be reported in seconds and percent of predicted normal for each walking speed. Changes in the number of seconds and percent of predicted normal for each speed from Baseline will be assessed.

Arm raising ability as measured by the weighted arm lift test will be reported as the total number of completed repetitions. Changes from Baseline in repetitions between the treatment arms will be assessed.

Functional disability as measured by the HIBM-FAS 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. Changes in the total score will be assessed.

7.6.2 Safety Measures

The safety measures in this study are:

- Incidence and frequency of AEs and SAEs
- Clinically significant changes from baseline in vital signs, physical and neurological examination findings and laboratory evaluations
- Interval history, including reported symptoms of increasing muscle weakness or pain, and incidence of falls

The analyses of safety will include all subjects who receive any study drug at any time during the study and provide any post-treatment safety information. Safety data will be periodically reviewed by the DMC.

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

Clinical laboratory data will be summarized by the type of laboratory test. The frequency and percentage of subjects who experience abnormal clinical laboratory results (i.e., outside of reference ranges) and/or clinically significant abnormalities after study drug administration will be presented for each clinical laboratory measurement. For each clinical laboratory measurement, descriptive statistics will be provided for Baseline and all subsequent post-treatment scheduled visits. Changes from Baseline to the post-treatment visits will also be provided. Descriptive statistics of vital signs, imaging assessments, and concomitant medications will also be provided in a similar manner.

The SAP will provide additional details on the planned statistical analysis.

7.6.3 Data Monitoring Committee

A DMC will be constituted for Study UX001-CL202 and will act in an advisory capacity to Ultragenyx to monitor the safety of SA-ER/SA-IR in subjects who participate in the study. The DMC may:

- Review plans for data monitoring.
- Evaluate the progress of the trial, study data quality, timeliness, subject recruitment, accrual and retention, subjects' risk versus potential benefit, and other factors that could affect the study outcome.
- Consider relevant information that may have an impact on the safety of the participants or the ethics of the study
- Make other recommendations to Ultragenyx concerning continuation, termination or other modifications of the study based on their observations of the study.

7.6.4 Determination of 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. As Part I of the study is intended to evaluate of 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.

Approximately 10 treatment-naïve 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.

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.

8 STUDY CONDUCT

8.1 Ethics

8.1.1 Institutional Review Board or Ethics Committee

The IRB/EC must be a properly constituted board or committee operating in accordance with 21 CFR Part 56, "Institutional Review Boards." This protocol, any protocol amendments, and the associated informed consent forms (ICFs) must be submitted to the IRB/EC for review and must be approved before screening of any subject into the study. Study drug may not be shipped to the investigator until Ultragenyx or its designee has received a copy of the letter or certificate of approval from the IRB/EC for the protocol and any protocol amendments, as applicable.

All subject recruitment and/or advertising information must be submitted to the IRB/EC and Ultragenyx or its designee for review and approval prior to implementation. IRB/EC approval of any protocol amendments must be received before any of the changes outlined in the amendments are put into effect, except when the amendment has been enacted to protect subject safety. In such cases, the chair of the IRB/EC should be notified immediately and the amendment forwarded to the IRB/EC for review and approval.

8.1.2 Ethical Conduct of Study

This protocol is written in accordance with the principles established by the 18th World Medical Association General Assembly (Helsinki, 1964) and subsequent amendments and clarifications adopted by the General Assemblies. The investigator will make every effort to assure the study described in this protocol is conducted in full conformance with those principles, current FDA regulations, ICH Good Clinical Practices (GCP) guidelines, and local ethical and regulatory requirements. Should a conflict arise, the investigator will follow whichever law or guideline affords the greater protection to the individual subject.
The investigator will also make sure he or she is thoroughly familiar with the appropriate administration and potential risks of administration of the study drug, as described in this protocol and the IB, prior to the initiation of the study.

8.1.3 Subject Information and Consent

Appropriate forms for documenting written informed consent will be provided by the investigator and reviewed and approved by Ultragenyx or its designee before submission to the IRB/EC. Ultragenyx or its designee must receive a copy of the IRB/EC's approval of the ICF before the shipment of study drug to the study site.

It is the investigator's responsibility to obtain signed written informed consent from each potential study subject prior to the conduct of any study procedures. This written informed consent will be obtained after the methods, objectives, requirements, and potential risks of the study have been fully explained to each potential subject. The investigator must explain

to each subject that the subject is completely free to refuse to enter the study or to withdraw from it at any time.

The method of obtaining and documenting informed consent and the contents of the ICF will comply with ICH GCP guidelines, the requirements of 21 CFR Part 50, "Protection of Human Subjects," the Health Insurance Portability and Accountability Act (HIPAA) regulations, and all other applicable regulatory requirements. Subjects will be given a copy of the signed ICF and will be provided any new information during the course of the study that might affect their continued participation in the study. The investigator or a qualified designee will be available to answer each subject's questions throughout the study, and all of the subject's questions must be answered to the subject's satisfaction. If the protocol is amended and the ICF is revised, each subject will be required to provide written informed consent again using the revised ICF.

Receipt of written informed consent will be documented in each potential subject's CRF. The signed ICF will remain in each subject's study file and must be available to the study monitor(s) at all times.

8.2 Investigators and Study Administrative Structure

Each investigator must provide Ultragenyx and/or its designee a completed and signed Form FDA 1572 and a Financial Disclosure Form. All sub-investigators must be listed on Form FDA 1572 and Financial Disclosure Forms must be completed for all sub-investigators listed on Form FDA 1572.

Ultragenyx and/or its designee will be responsible for managing and monitoring the clinical trial to ensure compliance with FDA and ICH GCP guidelines. Ultragenyx's trained designated representative (the monitor) will conduct regular visits to the clinical site, to perform source document verification. The monitor will verify the investigator's ongoing qualifications, inspect clinical site facilities, and inspect study records, including proof of IRB/EC review, with the stipulation that subject confidentiality will be maintained in accordance with local and federal regulations, including HIPAA requirements.

A Coordinating Investigator has been identified for this trial. The Coordinating Investigator is selected on the basis of active participation in the trial, thorough knowledge of the therapeutic area being studied, and the ability to interpret data. The Coordinating Investigator reads and signs the Clinical Study Report (CSR).

8.3 Investigational Product Accountability

While at the clinical site, study drug must be stored in a secure limited access location at controlled temperature as described in the IB and according to product packaging.
The storage facility must be available for inspection by the study monitor at any time during the study.

A drug accountability record must be maintained for all study drug received, dispensed, returned, designated for destruction, and/or lost during the study. This record must be kept current and made available to the study monitor for inspection. Following the close-out of the study, all unused study drug must be returned to Ultragenyx and/or its designee unless other instructions have been provided for final disposition of the study drug.

8.4 Data Handling and Record Keeping

8.4.1 Case Report Forms and Source Documents

The investigator is required to initiate and maintain, for each subject, an adequate and accurate case history that records all observations and other data related to the study for that subject. A validated electronic data capture (EDC) system will be used for entry of the data into electronic CRFs. Data must be recorded on CRFs approved by Ultragenyx or its designee. All information recorded on CRFs for this study must be consistent with the subject's source documentation.

Initial data entry and any changes to the data will be made only by Ultragenyx-authorized users, and data entries and changes will be captured in an electronic audit trail.
An explanation of any data change should be recorded in the CRF. All data entered in to the CRF must be verifiable; therefore, CRFs will be routinely checked for accuracy, completeness, and clarity and will be cross-checked for consistency with source documents, including laboratory test reports and other subject records by Ultragenyx or its designee.
The investigator must allow direct access to all source documents.

8.4.2 Data Quality Assurance

Monitoring and auditing procedures developed by Ultragenyx and/or its designee will be implemented to ensure compliance with FDA and ICH GCP guidelines.
Ultragenyx's designated representative (the monitor) will contact the investigator and conduct regular visits to the study site. The monitor will be expected and allowed to verify the investigator's qualifications, to inspect clinical site facilities, and to inspect study records, including proof of IRB/EC review, with the stipulation that subject confidentiality will be maintained in accordance with local and federal regulations, including HIPAA requirements. The monitor will also be responsible for confirming adherence to the study protocol, inspecting CRFs and source documents, and ensuring the integrity of the data. CRFs will be checked for accuracy, completeness, and clarity and will be cross-checked for consistency with source documents including progress notes, laboratory test reports and other subject records. Instances of missing or uninterruptable data will be resolved in coordination with the investigator.

The monitor will also investigate any questions concerning adherence to regulatory requirements. Any administrative concerns will be clarified and followed. The monitor will maintain contact with the site through frequent direct communications with the study site by e-mail, telephone, facsimile, and/or mail. The investigator and all other site personnel agree

to cooperate fully with the monitor and will work in good faith with the monitor to resolve any and all questions raised and any and all issues identified by the monitor.

The investigator understands that regulatory authorities, the IRB/EC, and/or Ultragenyx or its designees have the right to access all CRFs, source documents, and other study documentation for on-site audit or inspection and will retain this right from the start of the study to at least two years after the last approval of a marketing application or for at least two years after clinical development of the study drug for the indication being studied has been discontinued. The investigator is required to guaranty access to these documents and to cooperate with and support such audits and inspections.

8.4.3 Record Retention

All study records must be retained for at least 25 years after the end of the clinical trial or in accordance with national law. Subject files and other source data must be kept for the maximum period of time permitted by the hospital, institution or private practice, but not less than 25 years. Ultragenyx must be notified and will assist with retention should the Investigator/institution be unable to continue maintenance of subject files for the full 25 years. All study records must be stored in a secure and safe facility.

8.5 Reporting and Follow-up of Adverse Events

8.5.1 Definition of Adverse Events

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) products.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of expedited safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

Life-threatening AE or life-threatening suspected adverse reaction is an AE or suspected adverse reaction that, in the view of either the investigator or Ultragenyx, places the patient or subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

An SAE or serious suspected adverse reaction is an AE or suspected adverse reaction that at any dose, in the view of either the investigator or Ultragenyx, results in any of the following outcomes:

- Death

- A life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect

Note that hospitalizations planned prior to study enrollment (e.g., for elective surgeries) are not considered SAEs. Hospitalizations that occur for pre-existing conditions that are scheduled after study enrollment are considered SAEs.

Important medical events that may not result in death, be immediately life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

8.5.2 Severity of Adverse Events

Wherever possible, the severity of all AEs will be graded using the NCI CTCAE. The majority of AEs can be graded using this system.

If an AE cannot be graded using the CTCAE criteria, it should be graded as mild, moderate, severe, life-threatening, or death using the following definitions.

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

To make sure there is no confusion or misunderstanding of the difference between the terms "serious" and "severe," which are not synonymous, the following note of clarification is provided. The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious" which is based on subject/event outcome or action criteria usually associated

with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

8.5.3 Relationship of Adverse Events to Study Drug

The investigator will assess the potential relationship of the AE to study drug using the following descriptions.

- ***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 reasonable 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. That 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.

8.5.4 Adverse Event Reporting to Ultragenyx

8.5.4.1 General

All AEs (i.e. any new or worsening in severity or frequency of a preexisting condition) with onset after the subject signs consent for study participation must be promptly documented on the AE eCRF via the EDC system. The Principal Investigator is responsible for evaluating all AEs, obtaining supporting documents, and ensuring documentation of the event is adequate. Details of the AE must include severity, relationship to study drug, duration, and outcome.

All AEs will be collected from the time the subject signs the informed consent through 30 days following the last dose of study drug, or, if applicable, until the date the subject signs the informed consent for the open-label extension study, UX001-CL302, whichever occurs sooner. In addition for those subjects choosing not to enroll in UX001-CL302, the Investigator should report any AE that occurs more than 30 days following the last dose of study drug that is believed to have a reasonable possibility of being associated with study drug.

AEs ongoing after the defined follow-up period stated in the paragraph above should have a comment in the source document by the Investigator that the event has recovered, recovered with sequelae, or stabilized.

8.5.4.2 Serious Adverse Events, Serious Adverse Drug Reactions, and Requirements for Immediate Reporting

Any SAE that occurs at any time during the study, including a clinically significantly abnormal laboratory test result that is considered serious, must be reported within 24 hours of knowledge of the event to Ultragenyx or its designee. These requirements apply equally to all subjects, regardless of the study phase or the at-risk subject's treatment assignment or dosage. The reporting requirement for SAEs is from the time of signing of the ICF through 30 days following the last study drug administration.

SAEs will be reported by completing and submitting SAE report forms to Ultragenyx or its designee. Initial SAE reports must be followed by detailed descriptions. These should include copies of hospital case records and other documents when requested. Follow-up SAE information must be submitted in a timely manner as additional information becomes available. All SAEs regardless of relationship to study drug must be followed to resolution or stabilization if improvement is not expected.

A death occurring during the study, during the per-protocol follow-up period, or within 30 days after stopping treatment with the study drug must be reported to Ultragenyx or its designee within 24 hours of knowledge of the death whether or not it is considered treatment-related.

The investigator also must notify the IRB/EC of the occurrence of the SAE, in writing, as soon as is practicable and in accordance with IRB/EC requirements and local law. A copy of this notification must be provided to Ultragenyx or its designee.

8.5.4.3 Urgent Safety Reporting

The regulations governing clinical studies state that the sponsor and investigator are required to take appropriate urgent safety measures to protect subjects against any immediate hazards that may affect the safety of subjects, and that the appropriate regulatory bodies should be notified according to their respective regulations. According to the European Union (EU) Clinical Trial Directive 2001/20/EC, "…in the light of the circumstances, notably the occurrence of any new event relating to the conduct of the trial or the development of the investigational medicinal product where that new event is likely to affect the safety of the subjects, the sponsor and the investigator shall take appropriate urgent safety measures to protect the subjects against any immediate hazard. The sponsor shall forthwith inform the competent authorities of those new events and the measures taken and shall ensure that the Ethics Committee (EC) is notified at the same time." The reporting period for urgent safety issues is the period from the signing of the ICF through 30 days following the last dose of study drug. Investigators are required to report any urgent safety measures to Ultragenyx within 24 hours.

8.5.4.4 Adverse Drug Reaction Reporting

Ultragenyx or its designee will submit suspected unexpected serious adverse reactions (SUSAR) to appropriate Regulatory Authorities (including Competent Authorities in all Member States concerned), Ethics Committees, and Investigators as per local laws and regulations. Fatal and life-threatening SUSARs will be submitted no later than 7-calendar days of first knowledge of the event and follow-up information submitted within an additional eight (8) days. All other SUSARs will be submitted within 15-calendar days of first knowledge of the event.

Principal Investigators are required to report any urgent safety matters to Ultragenyx or its designee within 24 hours. Ultragenyx or its designee will inform the Regulatory Authorities, Ethics Committees, and Investigators of any events (e.g. change to the safety profile of UX001, major safety findings) that may occur during the clinical trial that do not fall within the definition of a SUSAR but may affect the safety of subjects participating in the clinical trials, as required, in accordance with applicable laws and regulations. The reporting period for urgent safety issues is the period from the signing of the ICF through 30 days following the last dose of study drug.

The investigator will notify the IRBs/Research Ethics Boards (REB)/ECs of SAEs and urgent safety matters, in accordance with IRB/REB/EC requirements and local laws and regulations. A copy of this notification must be provided to Ultragenyx or its designee.

Non-SUSARs will be maintained in the Ultragenyx safety database and provided in annual and/or periodic reports as per local laws and regulations. Ultragenyx or its designee will prepare and submit annual safety reports and/or other aggregate periodic summary reports to Regulatory Authorities and Ethics Committees, as per local laws and regulations.

8.5.4.5 Pregnancy in Subject or Partner

Pregnancies in subjects or partners must be reported within 24 hours of knowledge of the event to Ultragenyx or its designee. The reporting period for pregnancies is the period from the signing of the ICF through 30 days following the last dose of study drug.
Reported pregnancy of a subject or a subject's partner, while participating in the study, will be monitored for the full duration and/or followed until the outcome of the pregnancy is known. In the event of a pregnancy in the partner of a subject, the Investigator should make every effort to obtain the female partner's consent for release of protected health information. Pregnancy-associated SAEs will be processed and submitted, as necessary, as per the SUSAR reporting process (Section 8.5.4.4).

8.5.5 Safety Contact Information

Drug Safety	Medical Monitor
PrimeVigilance Fax: [redacted] e-mail: [redacted]	[redacted] MD Telephone: [redacted] e-mail: [redacted]

8.6 Financing and Insurance

Financing and insurance for this clinical trial will be addressed in clinical trial agreements with the study site.

8.7 Publication Policy

Any publication or presentation by the investigator and/or the Institution based on data or results resulting from the Ultragenyx study shall only be done in strict accordance with the Publication section in the Clinical Trial Agreement executed between Ultragenyx and the Institution and/or the investigator.

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10 SIGNATURE PAGE

Protocol Title: 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 Amendment 4

I have read Protocol UX001-CL202 Amendment 4. I agree to conduct the study as detailed in this protocol and in compliance with the Declaration of Helsinki, Good Clinical Practices (GCP), and all applicable regulatory requirements and guidelines.

Investigator Signature Date

Printed Name: _____

Accepted for the Sponsor:

As the Sponsor representative, I confirm that Ultragenyx will comply with all Sponsor obligations as detailed in all applicable regulations and guidelines. I will ensure the investigator is informed of all relevant information that becomes available during the conduct of this study.

[redacted]
[redacted] MD Date
[redacted]
Ultragenyx Pharmaceutical Inc.