STATISTICAL ANALYSIS PLAN

Title	**A Phase 1/2 First-in-human, 2-part Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Single Ascending Doses (Part 1: Open-label) and Repeat Doses (Part 2: Randomized, Double-blind, Placebo-controlled) of UX053 in Patients with GSDIII**
Protocol:	**UX053-CL101**
Investigational Product:	**UX053**
Phase:	**1/2**
Sponsor:	**Ultragenyx Pharmaceutical Inc.** **60 Leveroni Court** **Novato, CA, USA 94949**
Author:	PPD
Date:	**13 April 2023**
Version Number:	**1.0**

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ABBREVIATIONS

ADA	anti-drug antibody
AE	adverse event
AGL	amylo-α-1,6-glucosidase 4-alpha-glucanotransferase
AH50	alternative complement activity
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{inf}	AUC from time 0 to infinity
AUC_{last}	AUC from time 0 to the last measurable concentration
AUC_{tau}	AUC from time 0 to end of dosing period
BNP	B-type natriuretic peptide
BL	Baseline
BUN	blood urea nitrogen
CAP	controlled attenuation parameter
CBC/diff	complete blood count with differential
CH50	classical pathway complement activity
CK	creatinine kinase
CK-M/B	CK – muscle/brain
CL	clearance
C_{max}	maximum observed concentration
COVID-19	corona virus disease 2019
CRF	case report form
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
CYP2B6	cytochrome P450 2B6
DMC	Data Monitoring Committee
[redacted]	[redacted]
[redacted]	[redacted]
ECG	electrocardiogram
EDC	electronic data capture
EF	ejection fraction
EOS	end of study

ET	early termination
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FDA	Food and Drug Administration
FIH	first-in-human
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GDE	glycogen debranching enzyme
GGT	gamma-glutamyl transpeptidase
Glc_4	glucose tetrasaccharide
GNEM-FAS	GNE Myopathy Functional Activities Scale
GMP	Good Manufacturing Practices
GSD	glycogen storage disease
HDL	high density lipoprotein
HED	human equivalent dose
HEENT	head, eyes, ears, nose, and throat
Hex_4	hexose tetrasaccharide
HHD	handheld dynamometry
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IAR	infusion-associated reaction
IL-6	Interleukin-6
IND	Investigational New Drug (application)
INR	international normalized ratio
IP	investigational product
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IRT	interactive response technology
ISV	Initial Screening Visit
ITT	Intention to Treat
IV	intravenous
[redacted]	[redacted]

LDH	lactate dehydrogenase
LDL	low density lipoprotein
LDL-R	low density lipoprotein-receptor
LEC	lower extremity composite
LFTs	liver function tests
LNP	lipid nanoparticle
LV	left ventricular
LVH	left ventricular hypertrophy
LVM	left ventricular mass
LSM	liver stiffness measurement
MCH	mean corpuscular hemoglobin
MCHC	MCH concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model for End Stage Liver Disease
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
MTD	maximum tolerated dose
NOAEL	no-observed adverse effect level
NOV	Nutrition Optimization Visit
NYHA	New York Heart Association
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic(s)
[redacted]	[redacted]
PK	pharmacokinetic(s)
PP	Per Protocol
PROMIS	Patient-reported Outcomes Measurement Information System
PT	preferred term
PT/INR	prothrombin time/international normalized ratio
Q2W	every 2 weeks
R_{AUC}	accumulation ratio (calculated as AUC after repeat dose / AUC after a single dose)
RD	repeat dose
SAD	single ascending dose

SAE	serious adverse event
SAP	statistical analysis plan
sC5b-9	soluble Complement 5b-9
SF	shortening fraction
SF-36v2	Short Form Health Survey 36 version 2
SOC	System Organ Class
STV	Stabilization Visit
SUSAR	suspected unexpected serious adverse reaction
$T_{1/2}$	half life
TEAE	treatment-emergent adverse event
T_{last}	time of last measurable concentration
T_{max}	time of maximum observed concentration
UEC	upper extremity composite
ULN	upper limit of normal
US	United States
V_{ss}	volume of distribution at a steady state
WBC	white blood cell
WHO	World Health Organization

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within the UX053-CL101 Protocol dated 3 January 2022. Changes from these guidelines must be substantiated by sound statistical reasoning and documented in the clinical study report (CSR).

Should there be a difference between the SAP and the protocol with respect to data analysis, the SAP will take precedence over the protocol.

2 STUDY OBJECTIVE(S)

2.1 Primary Objective(s)

The primary objective of the study is to evaluate the safety of UX053 in adults with Glycogen Storage Disease (GSD) III.

2.2 Secondary Objective(s)

The secondary objective of the study is to characterize the PK of UX053 in adults with GSD III.

2.3 Tertiary Objectives

2.4 Exploratory Objectives

[redacted]

3 STUDY DESIGN

UX053-CL101 is a phase 1/2 FIH, 2-part study to evaluate the safety, tolerability, and PK of a single ascending dose (SAD; part 1) and repeat doses (RD; part 2) of UX053 in patients with GSD III (Figure 1). SAD and RD of UX053 are tested in separate cohorts. The SAD cohorts will be open-label, while the RD dose cohorts will be randomized, double-blind, and placebo-controlled.

Part 1: Single Ascending Dose Period

All subjects in the SAD Period will undergo a Screening Visit prior to their Baseline Visit. The SAD Period will consist of 4 cohorts, each consisting of 2-3 subjects, all of whom will receive open-label UX053 (Figure 1). The planned dose escalation will proceed from 0.05 mg/kg in cohort 1S, to 0.10 mg/kg in cohort 2S, to 0.20 mg/kg in cohort 3S, and to 0.30 mg/kg in cohort 4S. During the SAD Period, the independent Data Monitoring Committee (DMC) will review at least 2 weeks of safety data for all subjects within a cohort and the cumulative data from all subjects in prior dosing cohorts (when applicable) before deciding to proceed with the next SAD cohort. Dose levels for each cohort, in either the SAD or RD Period (described below), may be reduced depending on safety findings from prior cohorts. Each subject in the SAD Period of the study will be followed for 90 days after dosing. Additional subjects may be added to SAD cohorts at the discretion of Ultragenyx to further characterize safety and PD effects.

Part 2: Repeat Dose Period

All subjects in the RD Period will participate in a Screening Period (approximately 8 to 12 weeks), in which subjects will be screened for study eligibility and assessed for the need to optimize their diet based on nutrition guidelines for adults with GSD III based on expert recommendations (Table 1). Within the first 2 weeks after the Initial Screening Visit (ISV), the Investigator will review nutrition diary data to determine if nutrition optimization is needed. To facilitate progression through the screening period, subjects should be scheduled for a phone visit to occur 2 weeks after the ISV. If nutrition optimization is not needed, subjects will be informed at the 2-week follow-up ISV phone call that they can proceed to the Nutrition Stabilization Visit (STV).

If nutrition changes are needed, a 2 to 4 week period of nutrition optimization, including Nutrition Optimization Visits (NOV), will be performed to comply with GSD III-specific nutrition guidelines based on expert recommendations (Table 1). If nutrition optimization is needed, the 2-week follow-up ISV phone call becomes an NOV. During nutrition optimization, NOV phone visits may occur weekly or more frequently, nutrition diary and continual glucose monitoring (CGM) data may be reviewed, and safety laboratory tests may be obtained at the discretion of the Investigator. During NOVs, advice is provided to the subject on what dietary changes should be made and when safety labs, if any, will be

obtained. During nutrition optimization, the Investigator will review nutrition diaries and any available labs, ideally on a weekly basis, and determine when the subject has achieved nutritional compliance per protocol. When nutritional compliance per protocol is achieved, the site will call the subject to schedule the STV.

After nutrition changes are made (if necessary), all subjects will proceed to a nutrition STV that will occur at least 6 weeks prior to the Baseline Visit. No substantial nutrition changes should be made after the STV for the remainder of the study. Due to the staggered nature of the cohorts (described below), a subject may be in nutrition stabilization for longer than 6 weeks before their Baseline Visit; in such instances, the total duration of the Screening Period may exceed 12 weeks. Nutrition guidance and monitoring for this study was established with available health authority guidance, and greater detail is available in the Study Reference Manual.

Table 1: Nutrition Guidelines for Adults with GSD III

High protein intake with a target of ≥ 25% of total calories
Low complex carbohydrates intake with a target of < 50% of total calories
Minimal intake of simple sugars
Avoidance of fasting
Consideration of high-protein bedtime snack or a high-protein formula for overnight enteral feeding

Based on expert guidelines (Kishnani et al., 2010)

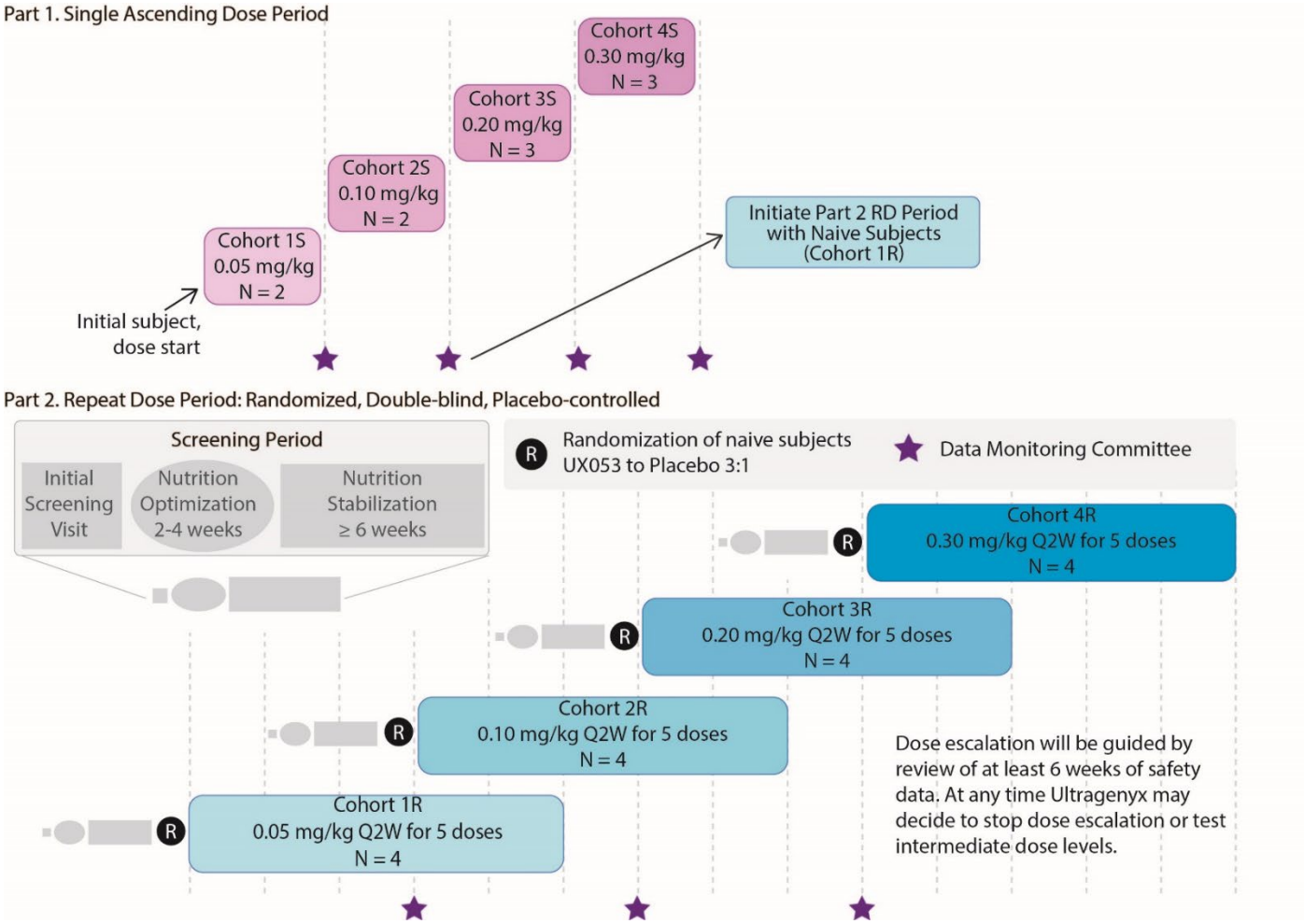
Mean weekly protein intake < 20% of total calorie intake and mean weekly carbohydrate intake ≥ 60% of total calorie intake for subjects will be considered protocol deviations, notwithstanding temporary changes to diet due to illness. The classification of such deviations will be determined by the magnitude, frequency, and duration of excursions beyond the specified guidelines.

In the RD Period, treatment-naive subjects will be randomized 3:1 to UX053 or placebo in ascending dose cohorts (4 subjects per cohort). Subjects enrolled in RD cohorts will receive study drug every 2 weeks (Q2W); a total of 5 doses of study drug are planned (Figure 1). Planned dose levels will be the same as for the SAD cohorts: 0.05 mg/kg in cohort 1R, 0.10 mg/kg in cohort 2R, 0.20 mg/kg in cohort 3R, and 0.30 mg/kg in cohort 4R. Dose escalation will be guided by DMC review of at least 6 weeks of safety data and any available PD and preliminary efficacy data from all subjects within a cohort and the cumulative data from all subjects in prior cohorts before proceeding with subsequent cohorts. At any time Ultragenyx may decide to stop dose escalation (ie, not initiate a planned dose cohort) or test intermediate dose levels. If safety data for all planned dose cohorts up to 0.30 mg/kg RD are acceptable and there is limited evidence of efficacy or PD effects through Week 12 from the 0.30 mg/kg RD cohort (4R), a 5th RD cohort receiving 0.45 mg/kg (cohort 5R not shown in Figure 1) may be added. Given the accumulation of safety data at this stage, no SAD cohort with 0.45 mg/kg is planned prior to the potential RD cohort 5R.

Cohort 1R may begin after review of safety data from cohort 2S. During the RD Period, an unblinded DMC will review at least 6 weeks of safety data from cohort 1R and all available data from prior cohorts before providing a recommendation for proceeding with cohort 2R. The same review and recommendation process will be used to determine the initiation for each of the remaining RD cohorts.

If a subject develops a treatment-emergent adverse event (TEAE)/serious TEAE ≥ Grade 3 that is considered by the Investigator to be related to study drug or an intolerable TEAE during the RD Period, subject-level dose reductions are allowed in consultation with the Medical Monitor, as outlined in the guidance provided in the Pharmacy Manual. Additionally, dose levels for each cohort may be reduced or higher dose cohorts may not be initiated, depending on safety and PD findings from prior cohorts. Ultragenyx will notify the DMC immediately if any subject experiences an event that satisfies subject-level stopping criteria or study-level stopping criteria. Additional subjects in blocks of 4 may be added to RD cohorts at the discretion of Ultragenyx to further characterize safety and PD effects, with input from the DMC.

Figure 1: UX053-CL101 Study Design



Note: Additional subjects may be included in any cohort at the discretion of Ultragenyx. Dose levels for each cohort, in either the SAD or RD Period, may be reduced depending on safety findings from prior cohorts. Additional cohort(s) at dose levels between 0.10 mg/kg to 0.45 mg/kg may also be included pending review of safety data.

Q2W, every 2 weeks; RD, Repeat Dose; SAD, Single Ascending Dose.

3.1 Study Population

Approximately 26-30 subjects will be enrolled in this study. The study will be conducted in adult subjects with a confirmed diagnosis of GSD III (ages ≥ 18 years). Subjects who are in participating in the RD Period are required to maintain a stable diet consistent with the nutrition guidelines based on expert recommendations after Nutrition Optimization during screening through the remainder of the study. Another key entry criteria is the exclusion of subjects with a history of liver transplant, history or cirrhosis, current hepatitis B or C infection or history of chronic hepatitis B or C infection, history of hepatocellular carcinoma. Additional entry criteria are outlined in the protocol.

3.2 Dosage and Administration

UX053 will be administered as an intravenous (IV) infusion over the course of at least 4 hours, with a slower rate of infusion for the first hour to minimize the risk of hypersensitivity or anaphylactoid-type reactions (refer to the Pharmacy Manual for additional infusion details). All subjects, including those treated with placebo, will receive premedication at least 1 hour prior to the infusion, consisting of oral paracetamol/acetaminophen (500 mg) or ibuprofen (400 to 800 mg), an H2 blocker (eg, famotidine 20 mg or equivalent dose of another H2 blocker), and an H1 blocker (eg, cetirizine 10 mg or equivalent dose of another H1 blocker). For the premedication, paracetamol/acetaminophen is preferred over ibuprofen. At the discretion of the Investigator, with input from Ultragenyx and the DMC, and based on the emerging safety profile of UX053, additional premedications and rescue medications may be used to reduce the risk and severity of immune reactions in RD cohorts.

In each cohort, subjects will be dosed sequentially with a minimum of 72 hours in between dosing for each subject's first dose. For example, the second subject in a cohort receives their first dose after a minimum of 72 hours after the first subject in the same cohort received their first dose. For subjects in the RD period, after sequential dosing for the first dose, subjects maintain a Q2W dosing regimen.

3.3 Blinding and Randomization Methods

In the SAD Period of the study, all subjects receive open-label UX053. In the RD Period of the study, subjects are randomized 3:1 to UX053 and Placebo, using an interactive response technology (IRT) system. The RD Period of the study is double-blind. Each subject will be assigned a unique identification number.

Blind conditions will be established so that Ultragenyx, the subject, and site personnel will not know the identity of a subject's treatment during the RD Period of the study. The only unblinded Ultragenyx members, who will be involved, as needed, in the preparation of the unblinded DMC outputs, are the Independent Statistician, Independent Statistical Programmer and Independent PK Analyst.

Randomization using an IRT system will ensure subjects in the RD Period of the study are blind to treatment. Due to the difference in opacities of the UX053 and the placebo, an unblinded pharmacist will prepare the study drug and an unblinded nurse will prepare the infusion before masking the infusion syringe and tubing with colored covers. Prespecified employees from Ultragenyx who do not have any contact with the investigative sites may also be unblinded as specified in the Blinding Plan.

All imaging assessments will be sent to central readers for evaluation. Readers will be blinded to the subject's treatment.

Treatment assignment for an individual subject should be unblinded by the Investigator only in an emergency, and only if when knowledge of the treatment assignment is urgently needed for the clinical management or welfare of the subject. Unblinding at the study site for any other reason will be considered a protocol deviation.

The Investigator is strongly encouraged to contact Ultragenyx before unblinding any subject's treatment assignment, but priority should be given to the safety of the subject.

3.4 Stratification Factors

Not Applicable.

3.5 Sample Size Considerations

The sample size for this study is based on practical considerations and is consistent with a FIH study in a rare disease population. Approximately 26 to 30 subjects will enroll in this study, with a minimum of 10 subjects in the SAD period, 16 subjects in the RD period, and with the option to enroll additional subjects in any cohort to further characterize safety or PD findings. With at least 10 subjects receiving UX053 in the SAD Period, there is an 89% chance of detecting a more common AE given the TEAE has a true incidence of 20%. If at least 22 subjects receive UX053 in both SAD and RD Periods, there is a 90% chance of detecting a TEAE with true incidence of 10%.

Subjects will be replaced at Ultragenyx's discretion only if they have not received study drug. Subjects will not be replaced if they have received any study drug.

3.6 Data Monitoring Committee

An independent DMC will be constituted with experts in metabolic liver disease, GSD III, and/or immune activation and will act in an advisory capacity to Ultragenyx. Additionally, at least one of the DMC members will have expertise concerning statistical methods used in the design and analysis of clinical trials.

The DMC will meet and review study data at the frequency defined and in accordance with the scope and objectives set forth in the DMC Charter. The DMC may provide advice to Ultragenyx regarding the safety of subjects, the ethics of the study and the continuing scientific validity of the study. The DMC may also make recommendations to Ultragenyx concerning continuation, termination or other modifications of the study based on their

review of data. Further details regarding the DMC can be found in the DMC charter, which will be available prior to the administration of investigational product (IP).

Ultragenyx will review the DMC recommendations and determine necessary actions that will be communicated accordingly to all stakeholders, eg, Regulatory Authorities, IRBs/IECs, and Investigators.

3.7 Planned Analyses

Analyses are planned for each data review described in the study design (Section 3). During the SAD Period, an unblinded DMC will review at least 2 weeks of safety data for all subjects within a cohort before deciding to proceed with the next SAD cohort. During the RD Period, the unblinded DMC will review at least 6 weeks of safety from cohort 1R and all available data from prior cohorts before providing a recommendation for proceeding with cohort 2R. The same review and recommendation process will be used to determine the initiation for each of the remaining RD cohorts.

4 STUDY ENDPOINTS AND COVARIATES

The full schedule of assessments is shown in Appendix 12.4.

4.1 Primary Endpoint(s)

- The incidence and severity of TEAEs, serious TEAEs, and related TEAEs.

4.2 Secondary Endpoint(s)

- PK parameters of *AGL* mRNA and ATX95, including T_{max}, C_{max}, AUC_{last}, AUC_{inf}, T_{last}, $T_{1/2}$, CL, V_{ss}.

4.3 Tertiary Endpoints

4.3.1 [redacted]

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4.3.2. PD/Efficacy Tertiary Endpoints

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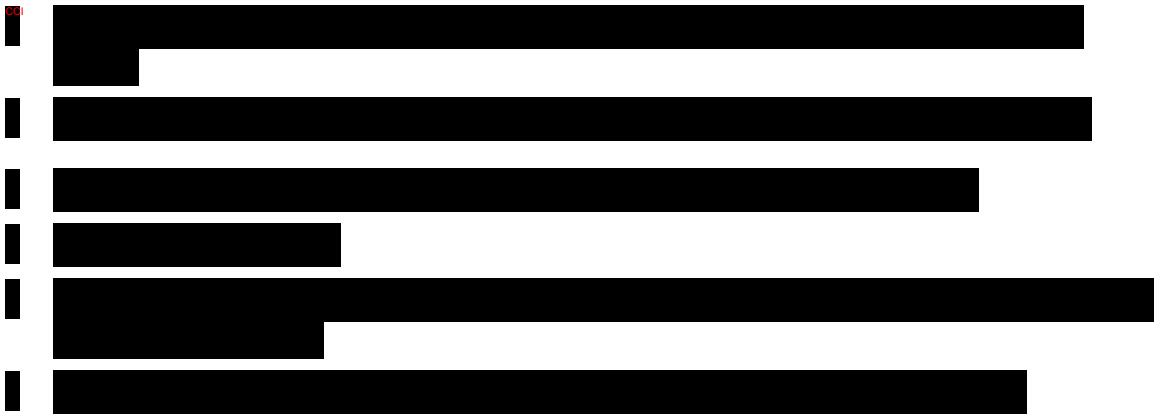

4.4 Exploratory Endpoints

4.5 Potential Covariate(s)

Not Applicable.

4.6 Subgroups

If a sufficient number of subjects with different disease subtypes (IIIa, IIIb, IIIc, and IIId) are enrolled, subgroup summaries by disease subtype may be provided at the discretion of Ultragenyx.

5 DEFINITIONS

5.1 Baseline

Baseline is defined as the last non-missing assessments prior to or on the date of initiation of the first dose of investigational product.

For nutrition diary data, baseline is defined as the average of all complete days (all values between screening and prior to dosing in SAD and between Stabilization Visit and prior to Dosing in RD). For CGM data, baseline is defined as the average of all daily measurements collected prior to the day of the first dose of IP administration.

5.2 Duration of exposure

Duration of exposure in days is defined as the last dose of investigational product – first dose of investigational product + 14 days.

5.3 Study Day and Study Period

If the visit date is on or after the first dose of IP administration:

- Study day = visit date – date of the first dose of IP administration + 1.

If the visit date is prior to the first dose of IP administration:

- Study day = visit date – date of the first dose of IP administration.

There are three analysis periods in this study: Screening (data collected before the first IP dose), Treatment (from first IP dose up to two weeks after the last IP dose) and Follow-up Period (from two weeks after the last IP dose up to the last measurement in the study).

5.4 Age

Unless specified, the age will be derived based on the informed consent date: Age = (Inform Consent Date – Birth Date +1)/365.25. The age will be rounded down to the nearest years, keeping 1 decimal place.

If birth date is missing, the birth date will be imputed to calculate age (See Section 7.3 for the algorithm to impute birth date).

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6 ANALYSIS POPULATIONS

6.1 Safety Analysis Set

Safety analysis set will include all enrolled subjects who received any volume of UX053. The primary analysis will be performed on the Safety Analysis Set.

6.2 Per Protocol Analysis Set

The Per Protocol (PP) Analysis Set will exclude subjects from Safety Analysis Set with major protocol deviations that may impact PD or efficacy analysis. Reasons for exclusion will be documented for each subject. If deemed appropriate, a sensitivity analysis will be performed on the PP Analysis Set.

6.3 Pharmacokinetics Analysis Set

The Pharmacokinetics (PK) Analysis Set is the subset of subjects in the Safety analysis set who have at least 1 evaluable IP concentration. The PK analysis set will be used for the analysis of the PK endpoints.

7 STATISTICAL METHODS OF ANALYSES

7.1 General Principles

Descriptive statistics will be provided for selected demographics, safety, PK, and PD data. If a sufficient number of subjects with different disease subtypes are enrolled, subgroup summaries by disease subtype may be provided at the discretion of Ultragenyx. Continuous variables will be summarized by number of subjects and mean, SD and/or SE, median, minimum, and maximum values. Categorical variables will be summarized by number and percentage of subjects. Data will be summarized with descriptive statistics for the Screening Period.

The subject-level and cohort-level graphs of endpoints measurements over time will highlight the three periods of the study: Screening (data collected before the first IP dose), Treatment (from first IP dose up to two weeks after the IP dose) and Follow-up Period (from two weeks after the IP dose up to the last measurement in the study).

Although they are eligible, it is expected that few patients with GSD IIIb, IIIc, or IIId will enroll. Subjects with GSD IIIb/c/d will participate in all assessments, including muscle imaging and function tests, and will be included in all safety analyses. Sensitivity analyses for cardiac and skeletal muscle endpoints that exclude patients with GSD IIIb/c/d may be conducted.

The analysis will be presented by cohort and total group (Table 3). All raw data obtained from the CRFs will be included in data listings.

Table 2 Analysis Groups in the SAD Period

Cohort 1	Cohort 2	Total

7.2 Subject Accountability

The number and percentage of subjects in study populations will be summarized for each period. Subject disposition table will also include the number of subjects screened, and enrolled. No formal statistical comparisons will be performed.

Screen-failure subjects (ie, subjects screened but not enrolled) and the associated reasons for failure to enroll will be tabulated overall for the Screened Population. The reasons for premature discontinuation from study as recorded on electronic case report forms (eCRFs) will be summarized.

7.3 Protocol Deviations

Major and Minor Protocol deviations will be separately summarized by analysis group in each period. Both major and minor protocol deviations will be listed.

At the discretion of the Ultragenyx, major protocol violations may result in the removal of a subject's data from the PP Analysis Set. Ultragenyx will be responsible for producing the final protocol violation file; this file will include a description of the protocol violation, and clearly identify whether this violation warrants exclusion from the PP Analysis Set.

7.4 Extent of Exposure

The cumulative dose administered and duration of exposure will be summarized overall and by cohort.

7.5 Demographic and Baseline Characteristics

Demographic parameters (age, age group, race, ethnicity, sex, weight, height, and body mass index) and other baseline characteristics will be summarized descriptively by period and cohort.

7.6 Prior and Concomitant Medication

Prior medications are defined as medications with start date and end date before the first dose of IP.

Concomitant medications are defined as medications with end date on or after the first dose of IP or ongoing.

Both prior and concomitant medications will be coded by drug name and therapeutic class using World Health Organization (WHO) Drug Dictionary, version B3 September 2020. If a subject took a specific medication multiple times or took multiple medications within a specific therapeutic class, that subject will be counted only once for the coded drug name or therapeutic class.

Prior and Concomitant medication will be presented by analysis group in each period.

7.7 Analysis of Primary Endpoints

The primary analysis endpoint is the incidence and severity of TEAEs, serious TEAEs, and related TEAEs in the SAD and RD Periods. The primary analyses will be based on Safety Analysis Set and displayed by analysis group in each period.

Adverse events will be coded by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA version 23.1 or above).

An AE (classified by preferred term) will be considered a treatment emergent adverse event (TEAE) if it occurred on or after the first dose of investigational product and was not present prior to the first dose, or it was present at the first dose but increased in severity or frequency. TEAE will be separately reported in SAD and RD Period.

Subject incidence of TEAEs and percentages will be tabulated as the following:

- TEAEs by analysis group in each period, SOC and PT (preferred term) (sorted by descending frequency in the pooled UX053 group by SOC and PT)
- Related TEAEs by analysis group in each period, SOC and PT (sorted by descending frequency by SOC and PT)
- Serious TEAEs by analysis group in each period, SOC and PT (sorted by descending frequency by SOC and PT)
- Serious Related TEAEs by analysis group in each period, SOC and PT (sorted by descending frequency by SOC and PT).
- TEAE by greatest severity, SOC and PT
- Deaths by analysis group in each period, SOC and PT (sorted by descending frequency by SOC and PT).
- TEAEs leading to discontinuation of study by analysis group in each period, SOC and PT (sorted by descending frequency by SOC and PT).

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

The severity of all AEs will be based on Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0, published on November 27, 2017, unless the AE is Cytokine Release Syndrome (CRS), in which case the AE will be graded by the American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading for CRS (Lee et al. 2019). If an AE cannot be graded based on CTCAE, the investigator will assign a severity based on 1 = mild, 2 = moderate, 3 = severe, 4 = life threatening, and 5 = Death.

7.8 Analysis of Secondary Endpoints

The secondary analysis endpoints are the PK parameters of *AGL* mRNA and ATX95, including T_{max}, C_{max}, AUC_{last}, AUC_{inf}, AUC_{tau} (RD Period only), R_{AUC} (RD Period only), T_{last}, $T_{1/2}$, CL, V_{ss} (SAD Period only). The secondary analyses will be analyzed for the PK Analysis Set and PP Analysis Set, if applicable.

Descriptive statistics will be summarized by number of subjects and arithmetic mean, SD, CV%, geometric mean, geometric SD, geometric CV%, median, minimum and maximum values for these PK parameters by analysis group in each applicable period, excluding total group in RD period. For T_{max}, only median, minimum and maximum values will be presented.

7.9 Analysis of Tertiary Endpoints

- [redacted]
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7.9.1 Nutrition Diary data

Nutrition diary data such as daily caloric intake (total kcalories), daily protein intake (grams and % of total caloric intake), daily total carbohydrate intake (grams and % of total caloric intake), daily non-cornstarch carbohydrate intake (grams and % of total caloric intake), daily cornstarch intake (grams, grams/kg and % of total caloric intake), daily fat intake (grams % of total caloric intake), and daily sugar intake (grams) will be listed by cohort and visit. Weekly descriptive summaries for all the nutrition diary components will be provided.

At least 3 complete days out of 7 will be necessary for the calculation of mean weekly intakes. For each week, if more than 4 days are either missing or not checked as complete, the nutrition diary data is considered missing for that week.

The following sensitivity analysis may be considered:

- Exclude data from days marked complete and with total caloric intake less than 500 kcals and
- Include data from days not marked as complete and with total caloric intake within one standard deviation of the average of days completed.

All data, regardless of completeness status, will be included in the listings.

7.10 Analysis of Exploratory Endpoints

[redacted]

[redacted]

7.11 Analysis of Other Endpoints

7.11.1 Vital Signs

Descriptive statistics for vital signs (systolic and diastolic blood pressures, heart rate, respiration rate, temperature (C) and weight) and changes from baseline values at each visit and at the end of study will be presented by analysis group in each period. Individual subject listing and individual plots over time of vital signs parameters during dosing and separately over time for all visits will be provided.

7.11.2 Electrocardiogram

Descriptive statistics for the absolute measurements and changes from baseline for selected ECG parameters will be reported. These include the following intervals: QT, QT corrected for heart rate, the time elapsed from the onset of atrial depolarization to the onset of ventricular depolarization (PR), and time elapsed for depolarization of the ventricles (QRS).

The frequency of subjects with a maximum increase from baseline in the QTc interval will be summarized according to the following categories: > 30 ms and > 60 ms. In addition, the frequency of subjects with QTc post dose values according to the following categories: > 450 ms, > 480 ms and > 500 ms, will be summarized.

The normality or abnormality of the ECG tracing will be summarized using shift tables of numbers of subjects who have a normal/abnormal ECG tracing at each scheduled time of assessment.

A listing of all ECG parameters including the overall assessment will also be created.

7.11.3 Urine Pregnancy Test

Urine pregnancy test results will be listed.

8 CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

Due to administrative reasons, the study terminated after enrollment of 4 subjects in Cohort 1S and 4 subjects in Cohort 2S. As such, only analyses specific to SAD cohorts 1S and 2S will be provided.

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10 APPENDICES

10.1 Handling of Missing and Incomplete Data

Missing clinical outcome data can occur for multiple reasons, including missed subject visits and scales or measures with missing item scores. Missing and incomplete data will be identified through the data quality review plan for this study. Missing and incomplete data will be identified for investigation, and possible resolution, by Data Management prior to the study database lock or snapshot.

Unless specified otherwise, only the observed data (not imputed data) will be presented in listings.

10.1.1 Missing Medical History Related Dates

- If only day is missing, impute 1.
- If month is missing, impute January 1st.
- If year is missing, then no imputation will be done; the date will be missing.
- If the imputed start date is earlier than the birth date, then the birth date will be used.
- If the imputed end date is earlier than the start date, the start date will be used.

10.1.2 Missing Birth Dates

To impute missing birth date, the following rules will be applied:

- If day is missing, impute 15.
- If month is missing, impute June.
- If year is missing, then no imputation will be done; the date will be missing.

If the imputed date is later than any study visit date/observed adverse event start date/ observed concomitant medication start date, then earliest available visit date/adverse event start date/ concomitant medication start date will be used without changing observed information.

10.1.3 Missing Date Imputation for Adverse Events and Concomitant Medications

The following conventions will be used to impute missing portions of dates for adverse events and concomitant medications. Note that the imputed values outlined here may not always provide the most conservative date.

Missing Start Dates

- If the day is unknown, then:
  - If the month and year match the first dose of investigational product start date month and year in this study, then impute the day of the first dose date.
  - Otherwise, assign the first day of the month.
- If the month is unknown, then:
  - If the year matches the year of the first dose of investigational product date in this study, then impute the month and day of the first dose date in this study.
  - Otherwise, assign 'January'
- If the year is unknown, then the date will not be imputed and will be assigned a missing value.

If the imputed date is earlier than birth date, then birth date will be used. If the imputed start date is later than the end date, then the start date will be set as the same date as the end date.

Missing Stop Dates (for AEs not ongoing)

- If the day is unknown, then assign the last day of the month.
- If the month is unknown, then assign 'December.'
- If the year is unknown, then the date will not be imputed and will be assigned a missing value, and the event will be considered ongoing. If the AE has been recorded as resolved/recovered, all efforts should be made to obtain the date from the Investigator.

  If the resulting end date is after the date of study completion / discontinuation/ data cutoff, set the imputed end date as close to the date of study completion / discontinuation/ data cutoff as possible without overwritten existing information

If the year is missing for the start date, and stop date (observed or imputed) is on or after the first dose or event is ongoing. The start date will be imputed as the first dose date.

10.1.4 Missing Causal Relationship to Investigational Product for Adverse Events

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

10.1.5 [redacted]

[redacted]

[redacted]

Table 3 [redacted]

[redacted]		

[redacted]

[redacted]

10.1.6 Missing Data for Other Efficacy Endpoints

When a change from baseline is assessed, missing data will not be imputed and only subjects with a baseline and at least 1 post-baseline measurement will be included in the analysis.

For the weekly nutrition diary data, at least 3 complete days out of 7 will be necessary for the calculation of mean weekly intakes. For each week, if more than 4 days are either missing or not checked as complete, the nutrition diary data is considered missing for that week.

[redacted]

10.1.7 Visit Time Windows

For an unscheduled visit that occurred after the first dose date of IP, the unscheduled visit will be mapped into the closest post-baseline study scheduled visit for the assessment based on the study day of the unscheduled visit, and the target study day of the scheduled visit of the assessment in the protocol. If the unscheduled visit has equal distance to the 2 study scheduled visits, it will be mapped to the later visit.

The unscheduled visit will be only mapped to study visit within each period during it occurs.

When there is more than 1 measurement mapped to the same scheduled visit (including the original measurement taken from the scheduled visit), the measurement taken on the scheduled visit will be used if it is not missing, otherwise the visit closest to the target day will be used. If more than 1 visit has equal distance to the target day, then the later visit will be used. If more than 1 measurement is collected on the same day, the time or sequence

number will be used to select the latest record. For listings and shift tables, all data points will be included.

Early termination visit will follow the same rule for unscheduled visit as described above.

10.2 Endpoints Derivation Details

10.2.1 [redacted]

[redacted]

10.2.1.1 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

10.2.1.2 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

10.2.1.3 [redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

10.2.1.4 [redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

10.2.1.5 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

10.3 Schedule of Evaluations:

Table 4: Schedule of Events for the Single Ascending Dose Period

Day (D) / Week (W)	Screening[a]	Treatment Period								EOS I (D90)/ ET[b]
		BL	Single Ascending Dose Period							
		D0	D1	D4	D7	D14	D21	D28	D42	
Visit Window Relative to Baseline	-	-	-	± 1 day		± 2 days				
Informed consent	X									
Inclusion/exclusion	X	X								
Drug Administration		X								
General Assessments										
General & GSD III-specific medical history	X									
COVID-19 testing	X									
Demographics	X									
Physical exam[c]	X	X[d]	X							X
Vital signs	X	X[e]	X	X	X	X	X	X	X	X
Height	X									
Weight	X	X[d]								X
Adverse events	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Pregnancy	X	X[d]						X	X	X

Day (D) / Week (W)	Screening[a]	Treatment Period								EOS I (D90)/ ET[b]
		BL	Single Ascending Dose Period							
		D0	D1	D4	D7	D14	D21	D28	D42	
Visit Window Relative to Baseline	-	-	-	± 1 day		± 2 days				
ATX95		X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]		
AGL mRNA		X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]		
Anti-drug antibodies		X[d]				X		X		X
Hepatitis B & C	X									
Hemoglobin A1C	X									
Serum CH50, AH50, sC5b-9, & IL-6		X[g]	X			X				
Plasma fibrinogen & d-dimer		X[g]	X			X				
Hematology	X	X[d]	X	X	X	X	X	X	X	X
Chemistry[h]	X	X[d]	X	X	X	X	X	X	X	X
Urinalysis[i]	X	X[d]	X	X	X	X	X	X	X	X
Serum CRP		X[d]	X	X	X	X	X	X	X	X
Liver										
Liver MRI	X									
Liver MRS[j]	X									
FibroScan or ultrasound elastography	X									
PT/INR[g]	X	X[d]	X		X					X
Serum HDL & LDL[k]	X	X[d]								
Cardiac										
Serum CK-M/B	X	X[d]								

Day (D) / Week (W)	Screening[a]	Treatment Period								EOS I (D90)/ ET[b]
		BL	Single Ascending Dose Period							
		D0	D1	D4	D7	D14	D21	D28	D42	
Visit Window Relative to Baseline	-	-	-	± 1 day		± 2 days				
Plasma BNP	X	X[d]								
Serum troponin I	X	X[d]								
ECG	X	X[d]	X							X
Skeletal Muscle & Strength										
Serum CK	X	X[c]								
Serum myoglobin	X	X[d]								
Calf MRS[j]	X									
HHD	X	X[d]								
Clinician- & Patient-reported Outcomes										
PROMIS questionnaires & SF-36v2		X[d]								
GNEM-FAS expanded version		X[d]								
Nutrition diary	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]
Exploratory Assessments										
Serum ketones	X	X[d]	X	X	X	X	X	X	X	X
Urine beta hydroxybutyrate[i]	X	X[d]	X	X	X	X	X	X	X	X
Serum biotinidase	X	X[d]								

Day (D) / Week (W)	Screening[a]	Treatment Period								EOS I (D90)/ ET[b]
		BL	Single Ascending Dose Period							
		D0	D1	D4	D7	D14	D21	D28	D42	
Visit Window Relative to Baseline	-	-	-	± 1 day		± 2 days				
CGM[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X
Plasma Glc[4]	X	X[d]								
Urine Glc[4][i]	X	X[d]			X					X
Whole blood RNA expression	X									
AGL variant analysis	X									
Blood Cell Pellet for Future Use	X	X[d]								
Serum & Plasma for Future Use[n]		X[d]			X			X		X

Footnotes continue on the following page.

a Screening assessments can be done over the course of multiple days. There must be 10 to 14 days between any assessments that are measured at both the Screening Visit and the BL Visit.

b In the event a subject has an ET, all efforts will be made to monitor the subject through the end of the study. At minimum, a safety follow-up phone call will occur within the 4 weeks following the subject's last treatment.

c Complete physical exam is required at the Screening, BL, and EOS I/ET Visits. Targeted physical exams may be performed at the D1 Visit.

d Assessments to be performed prior to dosing. The following assessments can be collected within a week prior to dosing, as long as there is 10 to 14 days between assessments that are repeated at the Screening Visit and the Baseline Visit: HHD, PROMIS questionnaires, SF-36v2, and GNEM-FAS expanded version.

e Refer to Table 6 for the timing of vital sign assessments during dosing.

f Refer to Table 7 for details of PK sampling. Please note that sample collections are marked for D1, D4, D7, D14, D21, and D28 in this table (Table 4) corresponding to a sample collection 1, 4, 7, 14, 21, and 28 days after infusion of UX053 on D0 as outlined in the final rows of the first column in Table 7.

g Sample to be collected pre-dose and at the end of the infusion. Post-infusion blood samples should be collected in the opposite arm of the infusion to avoid dilution.

h Close monitoring is required for subjects who develop elevations in ALT > 3x ULN and > 2x their baseline value, or elevation in ALT > 3x ULN with INR > 1.5. This includes repeating liver enzymes and INR within 48 hours and consideration of additional diagnostic tests such as liver ultrasound (Section 10.1.5).

i All efforts should be made for urine collections to be consistently taken from the first morning void.

j Liver and calf MRS are only required at sites with capability. Scanning for liver and calf MRS can be conducted immediately following the liver MRI.

k A 3 to 4 hour fasting period is preferred, but not required, prior to blood collection for serum HDL and LDL. All efforts should be made to obtain samples for HDL and LDL consistently for a given subject.

l The nutrition diary recordings should be recorded daily from the Screening Visit through the EOS I D90/ET Visit.

[m] The subject will receive CGM and HHG devices and will be trained on proper use at the Screening Visit. The CGM device will be worn continuously from the Screening Visit to the EOS I D90/ET Visit. If the CGM device alarm notifies a subject that their blood sugar is abnormally high or low or the subject suspects their blood sugar is abnormally high or low, the subject will need to check their blood sugar with a HHG device that will be provided by Ultragenyx at the Screening Visit (ISV for RD). When CGM data is being collected, all subjects will connect their CGM and HHG devices to a study-provided laptop weekly and upload CGM and HHG data. At remote visits, in conjunction with assessments performed by a home health nurse, the site will contact subjects by telephone or videoconference to confirm the CGM device is properly in use and data was uploaded; answer any questions regarding or help troubleshoot (if necessary) CGM device use; and review CGM data, HHG data (when applicable), and nutrition diary entries; these telephone calls will occur as needed for the SAD Period between Day 28 and Day 90/EOS I Visits. At in-clinic visits, a conversation between the site and the subject should occur to ensure CGM compliance and troubleshoot if needed.

[n] Serum and plasma samples will be collected for future biomarker assessments yet to be determined.

Note: White columns indicate in-clinic visits (Screening, BL D0, D1, and EOS I D90/ET). Gray columns indicate visits conducted at home by a home health nurse in conjunction with a phone call as needed (D4, D7, D14, D21, D28, and D42).

Note: Laboratory assessments included in chemistry, hematology, and urinalysis are provided in Appendix 3.

AGL, amylo-α-1,6-glucosidase 4-alpha-glucanotransferase; AH50, alternative complement activity; BL, baseline; BNP, B-Type Natriuretic Peptide; CGM, continuous glucose monitor; CH50, classical pathway complement activity; CK, creatinine kinase; CK-M/B, CK-muscle/brain; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; D, day; ECG, electrocardiogram; EOS, end of study; ET, early termination; GDE, glycogen debranching enzyme; Glc_4, glucose tetrasaccharide; GSD, glycogen storage disease; GNEM-FAS, GNE Myopathy Functional Activities Scale; HHD, handheld dynamometry; HHG, handheld glucometer; HDL, high density lipoprotein;IL-6, interleukin-6; LDL, low density lipoprotein; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; PROMIS, Patient-Reported Outcomes Measurement Information System; PBMC, peripheral blood mononuclear cell; PK, pharmacokinetic; PT/INR, prothrombin time/international normalized ratio; sC5b-9, soluble Complement 5b-9; SF-36v2, Short Form Health Survey 36 Version 2.

Table 6: Schedule of Vital Sign Assessments

Study Period	**SAD Period**	**RD Period**				
Time	**Day 0**	**Week 0**	**Week 2**	**Week 4**	**Week 6**	**Week 8**
Pre-Infusion						
Within 30 min of initiating the infusion	X	X	X	X	X	X
During infusion (4 hr infusion)						
15 min (± 5 min)	X	X	X	X	X	X
30 min (± 5 min)	X	X	X	X	X	X
45 min (± 5 min)	X	X	X	X	X	X
1 hr (± 10 min)	X	X	X	X	X	X
2 hr (± 10 min)	X	X	X	X	X	X
3 hr (± 10 min)	X	X	X	X	X	X
4 hr (± 10 min)	X	X	X	X	X	X
Post-infusion (24 hr monitoring)[a]						
5 hr (± 5 min)	X	X	X	X	X	X
6 hr (± 5 min)	X	X	X	X	X	X
7 hr (± 10 min)	X	X	X	X	X	X
8 hr (± 10 min)	X	X	X	X	X	X
9 hr (± 10 min)	X	X	X	X	X	X
10 hr (± 10 min)	X	X	X	X	X	X
16 hr (+/- 1hr)	X	X	X	X	X	X
24 hr (+/- 2hr)	X	X	X	X	X	X

hr, hour; min, minute; RD, Repeat Dose; SAD, Single Ascending Dose.
[a] All post-infusion time points refer to time from the beginning of the infusion.

Table 7: Schedule of PK Assessments during and following Treatment Infusion

Study Period	**SAD Period**		**RD Period**			
Sample Type	**Blood**	**Plasma**	**Blood**	**Plasma**	**Blood**	**Plasma**
Analyte	***AGL* mRNA**	**ATX95**	***AGL* mRNA**	**ATX95**	***AGL* mRNA**	**ATX95**
Infusion	**Day 0 Infusion**		**Week 0 Infusion**		**Week 8 Infusion**	
Pre-infusion						
Within 1 hr prior to initiating infusion	X	X	X	X	X	X

During infusion (4 hr infusion)						
1 hr (± 10 min)[a]	X	X	X	X	X	X
3 hr (± 10 min)	X	X	X	X	X	X
Post-infusion						
4 hr (± 10 min)[b]	X	X	X	X	X	X
4.5 hr (± 10 min)	X	X	X	X	X	X
5 hr (± 10 min)	X	X	X	X	X	X
6 hr (± 20 min)	X	X	X	X	X	X
8 hr (± 30 min)	X	X	X	X	X	X
10 hr (± 30 min)	X	X	X	X	X	X
24 hr (± 2 hr); Day 1	X	X	X	X	X	X
96 hr (± 24 hr); Day 4	X	X				
168 hr (± 24 hr); Day 7	X	X	X	X	X	X
336 hr (± 24 hr); Day 14	X	X	X[c]	X[c]	X	X
504 hr (± 24 hr); Day 21	X	X				
672 hr (± 24 hr); Day 28	X	X			X	X

10.4 Visit Window Example

SAD period:

Visit	Scheduled Visit Day	Window
Baseline	Day 0	< =1
Day 1	Day 1	[2]
Day 4	Day 4	[3, 5]
Day 7	Day 7	[6, 10]
Day 14	Day 14	[11, 17]
Day 21	Day 21	[18, 24]
Day 28	Day 28	[25, 34]
Day 42	Day 42	>=35