Statistical Analysis Plan

Protocol Version 4.0, 05 March 2020

Ultragenyx Pharmaceutical, Inc

A PHASE I/II OPEN LABEL, SINGLE-DOSE, GENE TRANSFER STUDY OF SCAAV9.U1A.HSGSH (ABO-102) IN PATIENTS WITH MIDDLE AND ADVANCED PHASES OF MPS IIIA DISEASE

Phase I/II

Prepared by: PPD Dec-15-2022

PPD
Statistician II
Pharmapace, Inc.

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Phase I/II

This Statistical Analysis Plan has been reviewed and approved by:

Dec-15-2022

Date

Dec-15-2022

Date

Dec-19-2022

Date

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AAV9	Adeno-Associated Viral Vector
CCI	[redacted]
AE	Adverse Event
ALT	Alanine Transaminase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CBC	Complete Blood Cell Count
CGI	Clinical Global Impression Improvement Scale
CRF	Case Report Forms
CSF	Cerebrospinal Fluid
CSHQ	Children's Sleep Habits Questionnaire
DA	Developmental Age
DNA	Deoxyribonucleic Acid
DQ	Development Quotient
CCI	[redacted]
ECG	Electrocardiogram
EDC	Electronic Data Capture
ELISA/ELISPOT	Enzyme-Linked Immunosorbent Assay / Enzyme-Linked Immunospot Assay
ERA	Environmental Risk Assessment
GAG	Glycosaminoglycan
GGT	Gamma-Glutamyl Transpeptidase
HIV	Human Immunodeficiency Virus
IMP	Investigational Medicinal Product
INR	International Normalized Ratio (also known as prothrombin time [PT])
ITT	Intention-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MPS	Mucopolysaccharidosis
CCI	[redacted]
PedsQL	Pediatric Quality of Life Inventory
PGI	Parent Global Impression Score
PI	Principal Investigator
PSI-4	Parenting Stress Index, 4th Edition

Abbreviation	Definition
PSSQ	Parent Symptoms Score Questionnaire
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
AAV9	Adeno-Associated Viral Vector
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
CCI	[redacted]
SD	Standard Deviation
SE	Standard Error
SGSH	N-Sulfoglucosamine Sulfohydrolase
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Events
vg/kg	Vector genomes per kilogram
WHODD	World Health Organization Drug Dictionary

1 INTRODUCTION

This document provides a detailed description of the statistical methods and procedures to be implemented during the analysis of Ultragenyx Pharmaceutical, Inc. ABO-102 ABT-003. The proposed methods and approaches to the data analysis should be viewed as flexible. If the data suggest and warrant it, deviations from this plan will be considered. However, any deviations from this statistical analysis plan (SAP) must be substantiated by sound statistical rationale and documented in the clinical study report.

2 STUDY OBJECTIVES

To evaluate the safety and efficacy of ABO-102 in patients with middle and advanced phases of Mucopolysaccharidosis (MPS) IIIA disease.

3 STUDY OVERVIEW

3.1 Study Design

This Phase I/II clinical trial is an open-label, single dose study of recombinant, self-complementary Adeno-Associated Viral Vector (AAV9) carrying the human N-sulfoglucosamine sulfohydrolase (hSGSH) gene under the control of the U1a promoter, scAAV9.U1a.hSGSH, also known as ABO-102, delivered one time intravenously to MPS IIIA participants. The target population includes MPSIIIA participants with a Developmental Quotient (DQ) lower than 60 in middle and advanced phases of the disease that would not be eligible for the clinical trial ABT-001. To ensure that both the middle phase and advanced phase of the disease are adequately represented in the study, a similar number of participants with a cognitive age equivalent of above 18 months (middle) and below 18 months (advanced), as assessed by the Bayley Scales of Infant and Toddler Development, will be enrolled.

During the active phase of the protocol, subjects will have 12 clinic visits and 5 labs visit over a two-year period. However, due to the study early termination, there will be at most 10 clinic visits and 5 lab visits over a one-year period. Unscheduled visits may be needed per the discretion of the investigator. Efficacy and safety will be evaluated.

3.2 Study Procedures and Visit Structure

After screening evaluations, eligible subjects will receive 3 x 10^{13} vg/kg of ABO-102 (scAAV9.U1a.hSGSH) delivered one time through a venous catheter inserted into a peripheral limb vein. A tapering course of prophylactic enteral prednisone or prednisolone will be administered. Subjects will remain in hospital following gene transfer for up to 48 hours post gene transfer for close monitoring, after which they will come back to the hospital for periodic visits over a two-year period. Subjects will be requested to participate in a separate 3 years long-term follow-up study (LTFU-ABO-102, EudraCT number 2019-

002979-34). If subjects do not consent to participate in the new study, the annual medical records will be collected for the same period.

Visits and procedures are summarized in the **Error! Reference source not found.** table 1 below.

Table 1. Schedule of Evaluations

STUDY TIMELINE OF EVENTS																			
Study Interval	**Screening**		**Pre Infusion Visit**	**Hospital Admission/ Vector Injection (Inpatient)**	**Inpatient**		**Follow-Up (Outpatient)**												
Visit #	**Visits 1**	**Visit 2**	**Visit 3**				**Visit 4**	**Visit 5**	**Visit 6**	**Labs**	**Visit 7**	**Labs**	**Visit 8**	**Labs**	**Labs**	**Labs**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**
Study Procedures	**Day -45 through -1**		**Day -1**	**Day 0**	**Day 1 (24 hrs)**	**Day 2 (48 hrs)**	**Day 7**	**Day 14**	**Day 30**	**Day 45**	**Day 60**	**Day 75**	**Day 90**	**2 weeks post steroids**	**Day 120**	**Day 150**	**Day 180**	**Month 12**	**Month 18**	**Month 24**
							+/- 2 days	+/- 2 days	+/- 3 days	+/- 3 days	+/- 7 days	+/- 3 days	+/- 7 days	+/- 7 days	+/- 7 days	+/- 7 days	+/- 21 days	+/- 30 days	+/- 30 days	+/- 30 days
Informed consent	X[1]																			
Demographics	X																			
Medical history	X						X	X	X		X		X				X	X	X	X
Adverse events	X	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	X
Head Circumference	X																X	X	X	X
Physical exam	X		X		X	X	X	X	X		X		X				X	X	X	X
Vital signs	X		X	X[2]	X	X	X	X	X		X		X				X	X	X	X
Height	X								X								X	X	X	X
Weight	X	X[16]	X						X		X		X				X	X	X	X
[redacted][3]	X																X	X	X	X
[redacted][3] of injection site				X[9]	X[9]															
Echocardiogram	X												X				X	X		X
ECG	X												X				X	X		X
45-minute EEG		X															X	X	X	X
Vineland scales assessment	X																X	X	X	X
Bayley scales assessment	X																X	X	X	X
Mullen scales assessment		X															X	X	X	X
Kaufman Battery assessment		X[11]															X[11]	X[11]	X[11]	X[11]
[redacted][3]		X															X	X	X	X
Neurocognitive Validity Form	X[12]	X[13]															X	X	X	X
Parent Global Impression Score																	X	X	X	X
Clinical Global Impression Improvement Score																	X	X	X	X
Parent Symptom Score Questionnaire	X																X	X	X	X
[redacted][3] 25m walk	X																X	X	X	X

STUDY TIMELINE OF EVENTS																				
Study Interval	**Screening**		**Pre Infusion Visit**	**Hospital Admission/ Vector Injection (Inpatient)**	**Inpatient**		**Follow-Up (Outpatient)**													
Visit #	**Visits 1**	**Visit 2**	**Visit 3**				**Visit 4**	**Visit 5**	**Visit 6**	**Labs**	**Visit 7**	**Labs**	**Visit 8**	**Labs**	**Labs**	**Labs**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**
Study Procedures	**Day -45 through -1**		**Day -1**	**Day 0**	**Day 1 (24 hrs)**	**Day 2 (48 hrs)**	**Day 7**	**Day 14**	**Day 30**	**Day 45**	**Day 60**	**Day 75**	**Day 90**	**2 weeks post steroids**	**Day 120**	**Day 150**	**Day 180**	**Month 12**	**Month 18**	**Month 24**
							+/- 2 days	+/- 2 days	+/- 3 days	+/- 3 days	+/- 7 days	+/- 3 days	+/- 7 days	+/- 7 days	+/- 7 days	+/- 7 days	+/- 21 days	+/- 30 days	+/- 30 days	+/- 30 days
CBC/Diff/Platelet	X		X		X		X	X	X				X				X	X	X	X
Electrolytes	X		X		X		X	X	X				X				X	X	X	X
Serum/plasma total protein, serum albumin	X		X		X		X	X	X				X				X	X	X	X
PT/INR/PTT	X		X		X		X	X	X				X				X	X	X	X
Creatinine/BUN	X		X		X		X	X	X				X				X	X	X	X
AST/ALT	X		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum/plasma GGT	X		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Alkaline phosphatase	X		X		X		X	X	X				X				X	X	X	X
Alpha-fetoprotein		X											X				X	X	X	X
Amylase	X		X		X		X	X	X	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]
Serum/plasma total bilirubin	X		X		X		X	X	X				X				X	X	X	X
Random Glucose	X		X		X		X	X	X				X				X	X	X	X
Troponin	X		X		X		X	X	X		X		X				X	X	X	X
Plasma and leukocyte SGSH enzyme activity levels	X						X	X	X		X		X				X	X	X	X
Urine GAG/heparan sulfate levels	X				X		X	X	X		X		X				X	X	X	X
Raw plasma heparan sulfate	X	X			X		X	X	X		X		X				X	X	X	X
Urinalysis	X				X		X	X	X				X				X	X	X	X
Vector Shedding Samples: Plasma, Urine, Feces, Saliva	X[5]	X[5]		X[6]	X	X	X	X	X		X[7]		X[7]				X[7]	X[7]	X[7]	X[7]
Urine or Serum pregnancy test (if applicable)	X			X														X		X
Gene sequening to confirm MPS IIIA diagnosis	X[8]																			
ELISpot	X						X	X	X	X[17]	X	X[17]	X	X[17]	X[17]		X	X	X	X
ELISA	X								X		X		X				X	X	X	X
Plasma biobanking		X		X			X	X	X		X		X				X	X	X	X
[redacted]	X				X		X	X	X		X						X	X	X	X
Serum nAbs	X																X	X		X
Serology: hepatitis B, C, and HIV		X																		
Sedation/Anesthesia		X		X[3]					X								X	X		X

STUDY TIMELINE OF EVENTS																			
Study Interval	**Screening**		**Pre Infusion Visit**	**Hospital Admission/ Vector Injection (Inpatient)**	**Inpatient**		**Follow-Up (Outpatient)**												
Visit #	**Visits 1**	**Visit 2**	**Visit 3**				**Visit 4**	**Visit 5**	**Visit 6**	**Labs**	**Visit 7**	**Labs**	**Visit 8**	**Labs**	**Labs**	**Labs**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**
Study Procedures	**Day -45 through -1**		**Day -1**	**Day 0**	**Day 1 (24 hrs)**	**Day 2 (48 hrs)**	**Day 7**	**Day 14**	**Day 30**	**Day 45**	**Day 60**	**Day 75**	**Day 90**	**2 weeks post steroids**	**Day 120**	**Day 150**	**Day 180**	**Month 12**	**Month 18**	**Month 24**
							+/- 2 days	+/- 2 days	+/- 3 days	+/- 3 days	+/- 7 days	+/- 3 days	+/- 7 days	+/- 7 days	+/- 7 days	+/- 7 days	+/- 21 days	+/- 30 days	+/- 30 days	+/- 30 days
Lumbar puncture		X							X								X	X		X
CSF enzyme activity & heparan sulfate levels		X							X								X	X		X
CSF protein, glucose, cell count and diff		X							X								X	X		X
[redacted]		X							X								X	X		X
[redacted]		X							X								X	X		X
CSF Biobanking		X							X								X	X		X
Brain MRI		X																X		X
[redacted]		X																X		X
Abdominal MRI		X							X								X	X		X
[redacted]		X[14]															X[18]	X[18]		X[18]
PedsQL Core Generic Scales	X																X	X	X	X
PedsQL Gastrointestinal Symptoms Scales	X																X	X	X	X
CSHQ	X																X[19]	X[19]	X[19]	X[19]
PSI4		X															X	X	X	X
Admit to Hospital				X																
Study agent administration				X																
Prophylactic Prednisolone/Prednisolone			X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]							
Participant Survey																				X[15]
	1. If there are changes to the study, parents will be re-consented at their next visit																			
	2. Day 0 Vital Signs (Heart rate, respiratory rate, pulse oximetry, temperature, and blood pressure) will be measured before and immediately after the infusion, and at least every five minutes during the infusion, and repeated at 15 minutes post-infusion. VS will be obtained hourly for 4 hours following the injection and then every 4 hours until discharge. Only the following time point will be recorded in EDC: Day 0 pre and post infusion; 1 hour post infusion, 2 hours, 4 hours, 8 hours, 12 hours, 24 hours and 48 hours post infusion.																			
	3. Need for sedation during gene transfer will be decided upon by the PI/designee, in discussion with the anesthesiologist and parent(s) on that day. Appropriate anesthesia (single event per visit) will be provided at Screening, Days 30 and 180, Month 12, and Month 24 with MRI imaging preceding lumbar puncture for safety.																			
	4. Prophylactic prednisolone/prednisone taper begins on Day -1 and is tapered according to AST, ALT, and ELISpot results. Anticipate that most participants will be on prednisolone for 90 to 120 days.																			
	5. Urine, feces and saliva vector shedding samples collected at Screening Visit 1. Plasma vector shedding sample collected at Screening Visit 2. If urine, feces and saliva are not obtained at Screening Visit 1, they will be obtained at Screening Visit 2.																			
	6. Plasma, urine, feces and saliva vector shedding samples collected at 4 and 8 hours post gene transfer.																			

STUDY TIMELINE OF EVENTS																				
Study Interval	**Screening**		**Pre Infusion Visit**	**Hospital Admission/ Vector Injection (Inpatient)**	**Inpatient**		**Follow-Up (Outpatient)**													
Visit #	**Visits 1**	**Visit 2**	**Visit 3**				**Visit 4**	**Visit 5**	**Visit 6**	**Labs**	**Visit 7**	**Labs**	**Visit 8**	**Labs**	**Labs**	**Labs**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**
Study Procedures	**Day -45 through -1**		**Day -1**	**Day 0**	**Day 1 (24 hrs)**	**Day 2 (48 hrs)**	**Day 7**	**Day 14**	**Day 30**	**Day 45**	**Day 60**	**Day 75**	**Day 90**	**2 weeks post steroids**	**Day 120**	**Day 150**	**Day 180**	**Month 12**	**Month 18**	**Month 24**
							+/- 2 days	+/- 2 days	+/- 3 days	+/- 3 days	+/- 7 days	+/- 3 days	+/- 7 days	+/- 7 days	+/- 7 days	+/- 7 days	+/- 21 days	+/- 30 days	+/- 30 days	+/- 30 days
	7. Vector shedding analysis post dosing will be performed on DNA isolated from different biological fluids (plasma, urine, saliva and feces) until two consecutive samples are negative for the presence of viral DNA for each specimen type.																			
	8. To be performed if not previously documented.																			
	9. [redacted] of the injection site to be taken prior to and after (approximately 24 h after infusion) vector administration.																			
	10. Further analysis only to be performed if previous results remain abnormal.																			
	11. Kaufman Battery will be used together with or replacing to the Mullen and/or Bayley scales based on developmental age results obtained with those scales.																			
	12. Neurocognitive Validity Form part 1 for Bayley Scales Infant and Toddler Development/Kaufman Battery and Vineland Adaptive Behavior Scale II- Survey form.																			
	13. Neurocognitive Validity Form part 2 for Mullen Scales of Early Learning, SBRS, PSI-4, PedsQL, and CSHQ if applicable																			
	[redacted]																			
	15. This survey should also be assessed in the last visit of screening failures and withdrawals.																			
	16 The weight obtained at Screening Visit 2 will be used to calculate the viral vector dose.																			
	17 To be performed if applicable based on results from previous visit.																			
	[redacted]																			
	19. This assessment should be performed only if a sleep problem has been identified during the initial evaluation at the Screening Visit 1 or the medical history suggests there is a problem affecting child's sleep.																			

4 STUDY ENDPOINTS

4.1 Primary Endpoints

- Product Safety as defined by the incidence, type and severity of treatment-related adverse events (AEs) and serious adverse events (SAEs) at Month 1, 2, 3, 6, 12
- Change from baseline in Cerebrospinal Fluid (CSF) heparan sulfate levels after treatment at Month 1, 6, 12
- Change from baseline in liver and/or spleen volumes after treatment, as measured by magnetic resonance imaging (MRI) at Month 1, 6, 12

4.2 Secondary Endpoints

- Change from baseline in plasma or urine glycosaminoglycans or heparan sulfate after treatment at Month 1, 6, 12
- Change from baseline in CSF or plasma or leukocyte SGSH enzyme activity levels after treatment at Month 1, 6, 12
- Change from baseline in brain volumes after treatment, as measured by MRI at Month 12
- Change from baseline in sleep pattern as measured by the modified Children's Sleep Habits Questionnaire (CSHQ) at Month 6, 12
- Change from baseline in Pediatric Quality of Life Inventory (PedsQL™) Core Generic Scales total score at Month 6, 12
- Change from baseline in parent quality of life, using the Parenting Stress Index, 4th Edition (PSI-4) at Month 6, 12
- Change from baseline in gastrointestinal symptoms using the PedsQL™ Gastrointestinal Symptoms Scales at Month 6, 12
- Parent Global Impression Score at Month 6, 12
- Clinical Global Impression Improvement Scale at Month 6, 12
- Change from baseline in Parent Symptoms Score Questionnaire at Month 6, 12
- Change from baseline in Body Mass Index (BMI) after treatment at Month 6, 12
- Incidence and change from baseline in abnormalities in standard awake 45-minutes-EEG monitoring at Month 6, 12
- Determination of vector shedding analysis in plasma, saliva, urine and feces will provide preliminary data for the Environmental Risk Assessment (ERA)

4.3 Exploratory Endpoints

- CCI
- [redacted]
- [redacted]
- [redacted]

- CCI [redacted]

5 ANALYSIS SETS

The following population will be defined for study summaries and analyses.

5.1 Intent-to-Treat Set (ITT)

The ITT Set will include all enrolled subjects who received ABO-102 and have at least one post-baseline efficacy measurement. Efficacy and safety analyses will be conducted based on the ITT Population.

The primary endpoints, secondary endpoints, CCI [redacted] endpoints will be analyzed using the ITT Set. At the time of the study termination, all 5 enrolled subjects were treated and had at least one post-baseline assessment. Therefore, the ITT Population is equivalent to all patients enrolled and will be used to evaluate both safety and efficacy data and for populating listings.

6 INTERIM ANALYSIS

Interim analysis will not be conducted due to the early study termination.

7 STUDY SUBJECTS

7.1 Subject Disposition

Subject disposition will be summarized and listed for the ITT Set. Counts and percentages of subjects who completed the trial or discontinued from the trial, as well as the discontinuation reasons, will be summarized. Subject enrollment by site will also be summarized.

Subject counts and percentages in each category will be provided in the summary table. The number of enrolled subjects will be used as the denominator for calculating percentages.

7.2 Demographic and Baseline Characteristics

Patient characteristics such as patient age, gender, race, ethnicity, and height, weight, and BMI at baseline will be summarized for the ITT Set.

Continuous variables (including: age, height, weight, BMI) will be summarized using descriptive statistics. Categorical variables (including: gender, race, ethnicity) will be summarized using group frequencies and percentages, as appropriate.

7.3 Medical History

Medical history will be summarized and listed for the ITT Set. Medical history will be coded using system organ class (SOC) and preferred terms from the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects within each SOC and PTs will be presented.

7.4 Inclusion/Exclusion Criteria

Inclusion and exclusion criteria failures will be provided in a listing for the ITT Set.

7.5 Protocol Deviations

Protocol deviations will be listed for the ITT Set. Protocol deviations may include but are not limited to deviation from informed consent, study procedure, study medication administration, or study restrictions. All protocol deviations will be reviewed by clinical and statistical teams to identify major protocol deviation prior to database lock.

Each protocol deviation will be classified into minor or major by subject matter experts based on ICH guidelines:

- Major: Major protocol deviations are defined as a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety or well-being.
- Minor: Minor protocol deviations are defined as any change, divergence, or departure from the study design or procedures defined in the protocol. These deviations would not be expected to adversely affect the rights, safety or well-being of the subjects and/or the quality and integrity of data.

7.6 Treatment Administration and Study Duration

The extent of treatment will be summarized as follows:

- Descriptive statistics for Duration of study (months)
- The number and percentage of patients in the following categories of duration of study: < 1 month, 1-< 2 months, 2-< 6 months, 6-< 12 months, 12+ months. Study duration (days) is defined as last visit date – dose date + 1, and 1 month = 30 days.

7.7 Concomitant Medications and Non-drug Treatments

Concomitant and non-drug treatments refer to all drug and non-drug treatments taken during the study, whether or not they are recorded at baseline (i.e., have stop day greater than or equal to day 1 relative to first dose of study drug). All medications will be classified using the latest version of World Health Organization Drug Dictionary (WHODD) coding

dictionary. The Anatomical Therapeutic Chemical (ATC) classification and preferred term will be included after coded.

ATC and preferred term will be used to list and summarize the data. If a subject records multiple drugs with the same preferred term, these shall be summarized once within the count for N (%) of subjects.

8 STATISTICAL METHODS OF ANALYSIS

8.1 General Considerations

Efficacy and Safety analyses will be performed using the ITT Set. All data collected during the study for the ITT Set will be included in data listings.

8.1.1 Descriptive Statistics

For descriptive statistical summaries, continuous variables will be summarized by number of observations (n), mean, standard deviation (SD), standard error (SE), median, minimum (MIN), and maximum (MAX). For categorical variables, frequency/count and percentage of subjects in each category will be provided.

Minimum and maximum values will be presented at the same precision as the original value. Mean and median values will be rounded to one decimal place greater than the precision of the original value. SDs and SEs will be rounded to two decimal places greater than the precision of the original value. Percentages for summarizing categorical data will be rounded to one decimal place.

The by-subject listings, including data at scheduled and unscheduled visits, will be sorted by subject number, and then by date/time of the records.

8.1.2 Defining the Study Baseline

Baseline is defined as the last non-missing measurement obtained prior to the administration of the study drug for all efficacy and safety measures. Screening visits will not be summarized and will only be listed, unless an assessment taken at screening is considered baseline by definition.

8.1.3 Handling of Multiple Observations

For efficacy data, if multiple records were recorded for the same protocol-defined visit, the re-assayed data will be used for data summary and analysis. Re-assayed data from unscheduled visits will be treated similarly.

If a subject has a scheduled visit, the assessment obtained at the scheduled visit will be used for data summary and analysis. Otherwise, if no scheduled visit assessment exists but at least one unscheduled visit assessment is available within the protocol-defined visit window, then the data at the latest unscheduled visit within the protocol-defined visit window will be used for data summary and analysis.

Any unscheduled visits that cannot be attributed to a scheduled visit according to a protocol-defined visit window will not be included in descriptive statistical summaries but will be presented in listings.

8.1.4 Handling of Missing or Partial Data

- Missing baseline values will not be imputed in any situation.
- Missing post-baseline values for by-visit data will be summarized using the protocol-defined visit windows. If a value is not available within a given window, no imputation will be done.
- If day of birth is missing, the 1st day of the month will be used to calculate chronological age.
- Missing data for AE relationship will be imputed as "Related".
- For incomplete dates for AEs or non-study medications, the missing component(s) will be assumed as the most conservative value(s) possible. Actual data values, as they appear in the clinical database, will be shown in the data listings. Rules for partial dates are described in the table below. If the AE year is missing or AE is ongoing, the end date will not be imputed. Note: in the table, D = day, M = month, and Y = year.

Parameter	Missing	Additional Conditions	Imputation
Start date for AEs	Time only		Time will not be imputed; but will be assumed to be after gene transfer time
	D only	M and Y same as M and Y of gene transfer date	Date of gene transfer
		M and/or Y not same as M and Y of gene transfer date	First day of non-missing month
	D and M	Y same as Y of gene transfer date	Date of gene transfer
		Y not same as Y of gene transfer date	Use January 1 of non-missing year
	M, D and Y	None – date completely missing	Date of gene transfer
Stop date for AEs	Time only		Time will not be imputed
	D only		Last day of non-missing month
	D and M		Use December 31 of non-missing year
	M, D and Y	Deceased	Date of death

Parameter	Missing	Additional Conditions	Imputation
		Not deceased	Date of the end of trial participation
Start date for concomitant meds	D only	M and Y same as M and Y of gene transfer date	Date of gene transfer
		M and/or Y not same as M and Y of gene transfer date	First day of non-missing month
	D and M	Y same as Y of gene transfer date	Date of gene transfer
		Y not same as Y of gene transfer date	Use January 1 of non-missing year
	M, D and Y	None – date completely missing	Date of gene transfer
Stop date for concomitant meds	D only	M and Y same as M and Y of gene transfer date	Last day of non-missing month
		M and/or Y not same as M and Y of gene transfer date	Last day of non-missing month
	D and M	Y same as Y of gene transfer date	Use December 31 of non-missing year
		Y not same as Y of gene transfer date	Use December 31 of non-missing year
	M, D and Y	None – date completely missing	Date will not be imputed

8.2 Efficacy Analyses

8.2.1 Analyses of Primary Efficacy Endpoints

- Change from baseline in CSF heparan sulfate levels after treatment at Month 1, 6, 12
- Change from baseline in liver and/or spleen volumes after treatment, as measured by MRI at Month 1, 6, 12

Descriptive statistics (N, mean, SD, SE, median, MIN, and MAX) will be calculated at baseline and each post-baseline time point for observed values and change from baseline.

8.2.2 Analyses of Secondary Efficacy Endpoints

- Change from baseline in plasma or urine glycosaminoglycans or heparan sulfate after treatment at Month 1, 6, 12
- Change from baseline in CSF or plasma or leukocyte SGSH enzyme activity levels after treatment at Month 1, 6, 12
- Change from baseline in brain volumes after treatment, as measured by MRI at Month 12
- Change from baseline in sleep pattern as measured by the modified CSHQ at Month 6, 12
- Change from baseline in PedsQL™ Core Generic Scales total score at Month 6, 12
- Change from baseline in parent quality of life, using the PSI-4 at Month 6, 12

- Change from baseline in gastrointestinal symptoms using the PedsQL™ Gastrointestinal Symptoms Scales at Month 6, 12
- Change from baseline in Parent Symptoms Score Questionnaire at Month 6, 12
- Parent Symptoms Score Questionnaire at Month 6, 12
- Parent Global Impression Score at Month 6, 12
- Clinical Global Impression Improvement Scale at Month 6, 12
- Incidence and change from baseline in abnormalities in standard awake 45-minutes-EEG monitoring at Month 6, 12

All of the above secondary efficacy endpoints will be presented by listings only.

- Determination of vector shedding analysis in plasma, saliva, urine and feces will provide preliminary data for the ERA

Vector shedding samples will continue to be collected and analyzed until two consecutive negative samples are collected or completion of the study by the subject, whichever comes first.

Observed values and change from baseline in copies per 1mL of specimen in plasma, saliva, urine and feces will be summarized descriptively at baseline and each post-baseline time point. Copies per 1mL of specimen in feces will be presented as a spaghetti plot over each visit by subject.

8.2.3 CCI

- CCI
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[redacted]

8.3 Safety Analyses

8.3.1 Adverse Events (AEs)

AE tables (except for AE overview table) will only include summaries of treatment-emergent adverse events (TEAE). TEAEs will be defined as those occurring during or after gene transfer on Visit 3 (Day 0). All AEs should be reviewed by Medical Monitor or Designee before the database is locked. All reported terms (investigator descriptions) for AEs should be reviewed by Medical Monitor or Designee before the database locked and will be coded

using the latest version of MedDRA. Number and percentage of subjects with TEAEs will be summarized by system organ classification and preferred term.

An overview table will be provided with the number and percent of the following categories, if applicable:

- Number of total AEs, TEAEs, and deaths
- Incidence of patients with at least one: TEAE, TEAEs related to study treatment (IMP-related TEAE), SAE, IMP-related SAE, non-serious TEAEs, and deaths
- Incidence of patients who discontinued due to: TEAE, IMP-related TEAE, SAE, and IMP-related SAE
- Incidence of deaths and deaths due to IMP-related TEAE

TEAEs leading to discontinuation of study drug, IMP-related TEAE, serious TEAEs, non-serious TEAEs, and TEAEs by severity will be summarized and listed. Deaths will be listed, if any.

AEs occurring prior to gene transfer are defined as pre-treatment AEs and will be listed only.

AEs with relationship 'Possible', 'Probable', or 'Definitely' to IMP are defined as AEs related to study treatment.

Safety primary endpoint

- Product Safety as defined by the incidence, type and severity of treatment-related AEs and SAEs at Month 1, 2, 3, 6, 12

Product safety will be assessed by the incidences of treatment-related AEs and SAEs type and severity at each time point (<1 month, 1-<2 months, 2-< 3 months, 3-<6 months, 6-<12 months, and >= 12 months from treatment date to AE onset date). Counts of subjects and percentages will be provided for baseline and post-baseline visits. Treatment-related AE is defined as AE that is 'Possible', 'Probable' or 'Definitely' related to study drug.

8.3.2 Clinical Laboratory Evaluations

Hematologic, chemistry, coagulation and urinalysis laboratory measurements will be summarized by visit. For the continuous data, descriptive statistics (n, mean, SD, median, minimum, maximum) in change (absolute and percent) will be presented. For the categorical data, the number and the percentage of subjects for each observed category under each analyte will be summarized.

8.3.3 Vital Signs and Physical Examination

Vital Signs

Vital signs will include weight, height, BMI, head circumference, body temperature, heart rate, respiratory rate, pulse oximetry, and systolic and diastolic blood pressure for all time

points. Summary statistics will be calculated at baseline and follow-up time points as well as the nominal and percent changes from baseline for each visit.

Physical Exams

Adverse physical examination changes are captured as AEs. Physical Exam findings and vital signs will be included in the listings. Physical exam findings will be listed at each visit.

8.3.4 Electrocardiogram (ECG) and Echocardiogram

Electrocardiogram

The following ECG measurements are taken in 12-lead ECG at Screening/Visit 1, Visit 8 (Day 90), Visit 9 (Day 180), Visit 10 (Month 12):

- Overall evaluation (normal; abnormal-clinically significant; abnormal-not clinically significant).

The number and percentage of individuals on overall evaluation with normal, abnormal-not clinically significant, abnormal-clinically significant ECG's results will be tabulated.

All reported abnormal values will be listed.

Echocardiogram

The following measurements are taken at Screening/Visit 1, Visit 8 (Day 90), Visit 9 (Day 180), Visit 10 (Month 12):

- Fractional shortening %
- LV Ejection fraction %
- Overall evaluation (normal; abnormal-clinically significant; abnormal-not clinically significant)

For the continuous data, descriptive statistics (n, mean, standard deviation, median, minimum, maximum) in raw and change (absolute and percent) will be presented.

The number and percentage of individuals on overall evaluation with normal, abnormal-not clinically significant, abnormal-clinically significant results will be tabulated.

All reported abnormal values will be listed.

8.4 Definitions and Derived Variables

8.4.1 Chronological Age

Chronological Age (months) will be calculated using the Date of Birth and the testing date.

Chronological Age = (Testing Date – Date of Birth +1) / 30

8.4.2 Body Mass Index (BMI)

BMI is the subject's body weight in kilograms divided by the square of the subject's height in meters.

BMI = weight in kilograms / (height in meters)^2

8.4.3 Mullen Developmental Age (DA) and Developmental Quotient (DQ)

Mullen Developmental Age (in months) is calculated as the mean of the age equivalents obtained from the scores of four out of the five domains of the scale except Gross motor.

Mullen DA = (Fine Motor Age Eq + Receptive Language Age Eq + Expressive Language Age Eq + Visual Reception Age Eq) / 4

Mullen DQ = (Mullen DA / Chronological Age) * 100

8.4.4 Vineland Adaptive Age Equivalent and Adaptive Developmental Quotient (DQ)

Vineland Adaptive Developmental (in months) is calculated using the Age Equivalents from the 11 subdomains of the scale. Instead of using the mean of the 11 subdomains, the subdomains are first grouped into four areas, and the Adaptive Age Equivalent is calculated from the mean of those four areas. Example:

- Communication Age Equivalent is calculated as the mean of: Receptive Age Eq + Expressive Age Eq + Written Age Eq
- Daily living skills Age Equivalent is calculated as the mean of: Personal Age Eq + Domestic Age Eq + Community Age Eq
- Socialization Age Eq is calculated as the mean of: Interpersonal relationships Age Eq + Play and Leisure Time Age Eq + Copying Skills Age Eq
- Motor Skills Age Eq is calculated as the mean of: Fine Age Eq

Vineland Adaptive Age Equivalent = (Communication Age Eq + Daily living skills Age Eq + Socialization Age Eq + Motor Skills Age Eq) / 4

Vineland DQ = (Vineland Age equivalent / Chronological Age) * 100

The Vineland Adaptive AE and Adaptive DQ scores will be collected through Case Report Forms (CRF) and will not be recalculated during programming.

8.4.5 Cognitive Bayley Developmental Age (DA) and Cognitive Developmental Quotient (DQ)

Mean Developmental Age (DA) = (Developmental Age for Cognitive + Developmental Age for Receptive Language + Developmental Age for Expressive Language + Developmental Age for Fine Motor) / 4

Cognitive DQ = (Cognitive Developmental Age / Chronological age) *100

DQ = (Mean Developmental Age/ Chronological age) *100

8.4.6 CCI

[redacted].

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- [redacted]
- [redacted]
- [redacted]

CCI [redacted]

8.4.7 Modified Children's Sleep Habits Questionnaire (CSHQ)

CSHQ total score is calculated by adding all the 8 subscores. All scores will be collected through CRF and will not be recalculated during programming.

8.4.8 Pediatric Quality of Life Inventory (PedsQL™)

The PedsQL Core Generic Scales will use PedsQL Core Total Score in CRF. The PedsQL Gastrointestinal Symptoms Scales will use PedsQL GI Symptoms Score in CRF.

8.4.9 Parenting Stress Index, 4th Edition (PSI-4)

Total raw score is calculated by adding the three subscores: Raw score = (PD) + (P-CDI) + (DC). The raw score will be converted to total stress score. All scores will be collected through CRF and will not be recalculated during programming.

8.4.10 Parent Global Impression Score (PGI)

PGI total score is calculated by adding all the 9 subscores. All scores will be collected through CRF and will not be recalculated during programming.

8.4.11 Clinical Global Impression Improvement (CGI)

The Clinical Global Impression Improvement Scale Score will use CGI Global Improvement score in CRF.

8.4.12 Parent Symptoms Score Questionnaire (PSSQ)

The Parent Symptoms Score Questionnaire contains 29 symptoms with an indicator of whether the symptom was present or absent, and if present, a ranking value. Number of patients who have the symptom and average rank for each symptom will be calculated by visit.

9 STATISTICAL SOFTWARE

All statistical analyses will be performed using SAS® version 9.4.

10 CHANGES FROM THE PROTOCOL

Due to the study early termination and only 5 subjects being enrolled, there will be no comparison to natural history study data.