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

Protocol Number: ABT-003

Version: 5.0, 22 September 2022

Product number:	ABO-102/UX111
Indication:	Mucopolysaccharidosis (MPS) IIIA
IND Number:	16850
EudraCT Number:	2018-000504-42
Sponsor:	Ultragenyx Pharmaceutical Inc. 60 Leveroni Court Novato, CA 94949 USA
Medical Monitor:	PPD

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLES

DOCUMENT HISTORY	
Document	**Date**
Original Clinical Trial Protocol v1.0	09Mar2018
Clinical Trial Protocol v2.0	12Apr2018
Clinical Trial Protocol v3.0	25Feb2019
Clinical Trial Protocol v4.0	05Mar2020

RATIONALE FOR THE PROTOCOL AMENDMENTS	
Protocol Version	**Description of Changes**
1.0	• Original protocol sent to FDA in IND 16850
2.0	• Added clarification to Secondary Outcome and Statistical Analysis that the Vineland Adaptive Behavior Scale II will be used • Clarified sample types for lab work to include: o Screening, Pre-infusion, Days 7, 14, 30, 90, 180, Months 12, 18, 24 visits: Serum/plasma total protein, AST, ALT, serum/plasma GGT, Serum/plasma total bilirubin o Day 1: Serum/plasma total bilirubin o Days 45, 60, 75, 120, 150, 2-weeks post steroid taper visits: Aspartate aminotransferase (AST), alanine transaminase (ALT), serum/plasma gamma-glutamyl transpeptidase (serum/plasma GGT) • Clarified for Screening, Day 30, 180, Month 12 visit regarding abdominal MRI to measure liver and spleen volumes • Clarified Section 6.3.1 Day of Gene Transfer (Day 0) instructions • Section 6.4.1.1, added clarification regarding tapering instructions • Added assessment at Day 30 for amylase levels • Section 7.4.1, deleted 'recession' • Section 7.4.3: Updated with new data available • Updated References
3.0	• Separated signature pages for Sponsor and Principal Investigator • Added tables to describe document history • Clarified clinical phase of study • Clarified study population and updated inclusion/exclusion criteria • Updated primary, secondary and exploratory outcomes • Reorganized the introduction sections according to a new template • Removed age criteria • Added inclusion criterion: Cognitive Development Quotient (DQ) lower than 60 • Added exclusion criteria: • Participants with concomitant illness or requirement for chronic drug treatment that in the opinion of the PI creates unnecessary risks for gene transfer, or precludes the child from participating in the protocol assessments and follow up • Participants with a positive response for the ELISPOT for T-cell responses to AAV9

RATIONALE FOR THE PROTOCOL AMENDMENTS	
	• Any vaccination with viral attenuated vaccines less than 30 days prior to the scheduled date of treatment (and use of prednisolone) • Previous treatment by Haematopoietic Stem Cell transplantation • Previous participation in a gene/cell therapy or ERT clinical trial • Deleted exclusion criteria: • Prior treatment with SGSH enzyme replacement therapy (ERT) • Updated Primary and Secondary Outcome Measures and added Exploratory Measures • Remove the Dose Limiting Toxicity section • Included a section with Dosing New Participants, to clarify that patients will be treated with a 14-day interval • Modify the Stopping Rules, to indicate that study will be halted if 2 or more SAEs (not Grade III AEs) are reported. • Deleted neurocognitive assessment using Leiter scale • Inclusion of a neurocognitive validity form • Inclusion of the Vineland, Bayley, Mullen and Kaufman (depending on developmental age) scale neurocognitive assessment for all participants participating. • Added PedsQL, PSI-4 and CSHQ clinical questionnaires. • Added CCI Parent Global Impression Score, Clinical Global Impression Improvement Scale and Parent Symptom Score Questionnaire • CCI . • Changed the patient weight for dosing to the one obtained in Screening visit 2. • CCI • Provided more detailed information about the vital sign collection after treatment • Changed some study visit windows to allow more flexibility. • CCI • Added CSF biobanking • CCI • Included a participant questionnaire to collect information on the quality of the service provided by vendors interacting with participants. • Reorganized the safety sections according to a new template • Limited the SAEs to those who are following the regulatory definition by ICH and not all grade 3, 4 or 5. • Replaced terminology of ‘subject’ with ‘participant’ • Added 60-minute EEG at Months, 6, 2, 18, and 24
4.0	• Added inclusion criterion: ‘Age range of 2 years up to 18 years (excluded)’. • Updated the version of CTCAE to be referenced for AEs, to v4.03. • CCI • CCI . • Clarification of the scale to be used for the two arms in the study above and below 18 months of chronological age. • Removed medical history assessment at Visits 2 and 3. • Added urine pregnancy test (if applicable) at Day 0, Months 12 and 24.

RATIONALE FOR THE PROTOCOL AMENDMENTS	
	• Added troponin in the panel of labs, to be assessed at Visit 1, Days -1 and 1, and at Visits 4 to 12. • ELISpot assessment: removed from Day 7 and added at Days 45, 75, 120, and at 2-weeks post-steroid, if needed based on previous results. • Corrected several inconsistencies between the schedule of evaluations table and Section 5, study procedures. • Revised the EEG assessment from 60-minute EEG to 45-minute EEG. • CCI [redacted] • Added the acceptable method of contraception for the study and instructions on reporting of pregnancy during the study. • Specified the prohibited medications for the study and instructions on capturing concomitant medication/therapy. • Specified that the blood sample schedule and collection allows for a maximum blood volume of 35 ml per study visit, with flexibility to the sites to reduce volume as per site policy if needed and that additional ad-hoc analysis on blood samples collected at any particular visit may be performed at the discretion of the PI. • Specified the order of certain scales to be administered and the provision for use of an external qualified and trained rater, if the family signed the consent annex. • Added that prophylactic enteral prednisone or prednisolone will not be provided by the Sponsor; the standard of care at the site/country should be used for prophylaxis. • Revised the wording on long-term monitoring to include the long-term follow-up study designed to enroll participants who complete the current study. • Provided rationale on the choice of primary and secondary outcomes. • Clarified the definitions and reporting of AEs, SAEs and SAR. • Clarified the stopping/discontinuation rules for the study (Section 7.2). • Added that the date of birth and age of the participant at screening will be collected to ensure that the appropriate age-based assessments are performed throughout the study. Demographic data including age, gender, race and date of birth will be collect at Visit 1. • Clarified the DSMB roles and requirements, including an update to the minimum number of members required, from 3 to 4 members. • Several editorial changes for clarity and correction of errors throughout the protocol.
5.0	• Study sponsor changed to Ultragenyx Pharmaceutical Inc. • Indicated that ABO-102 is also known as UX111 • Medical Monitor changed to PPD [redacted] • Long-term monitoring language updated to indicate a minimum follow-up period of 3 years in Study LTFU-ABO-102

1. PROTOCOL SYNOPSIS

Title	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
Protocol Number	ABT-003
Number of participants	Approximately n = 12 Target population includes MPSIIIA participants with a DQ lower than 60 in middle and advanced phases of the MPSIIIA 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.
Clinical Phase	Phase I/II trial
Number of Centers	Up to five (5) centers worldwide
Study Objectives	To evaluate the safety and efficacy of ABO-102 (also known as UX111) in patients with middle and advanced phases of MPS IIIA disease.
Study Design	Open-label, single-dose clinical trial of ABO-102 (scAAV9.U1a.hSGSH) injected intravenously through a peripheral limb vein
Study Population	**Inclusion Criteria** 1. Diagnosis of MPS IIIA confirmed by the following methods: a. No detectable or significantly reduced SGSH enzyme activity by leukocyte assay, and b. Genomic DNA analysis demonstrating homozygous or compound heterozygous mutations in the SGSH gene 2. Cognitive Development Quotient (DQ) lower than 60 (calculated by Bayley Scales of Infant and Toddler Development - Third Edition) 3. Must be ambulatory, though may receive assistance with ambulation 4. Age range of 2 years up to 18 years (excluded). **Exclusion Criteria** 1. Inability to participate in the clinical evaluation as determined by Principal Investigator 2. Identification of two nonsense or null variants on genetic testing of the SGSH gene 3. At least one S298P mutation in the SGSH gene 4. Has evidence of an attenuated phenotype of MPS IIIA 5. Presence of a concomitant medical condition that precludes lumbar puncture or use of anesthetics 6. Active viral infection based on clinical observations 7. Concomitant illness or requirement for chronic drug treatment that in the opinion of the PI creates unnecessary risks for gene transfer,

	or precludes the child from participating in the protocol assessments and follow up 8. Participants with total anti-AAV9 antibody titers ≥ 1:100 as determined by ELISA binding immunoassay 9. Participants with a positive response for the ELISPOT for T-cell responses to AAV9 10. Serology consistent with exposure to HIV, or serology consistent with active hepatitis B or C infection 11. Bleeding disorder or any other medical condition or circumstance in which a lumbar puncture (for collection of CSF) is contraindicated according to local institutional policy 12. Visual or hearing impairment sufficient to preclude cooperation with neurodevelopmental testing 13. Any item (braces, etc.) which would exclude the participant from being able to undergo MRI according to local institutional policy 14. Any other situation that precludes the participant from undergoing procedures required in this study 15. Participants with cardiomyopathy or significant congenital heart abnormalities 16. The presence of significant non-MPS IlIA related CNS impairment or behavioral disturbances that would confound the scientific rigor or interpretation of results of the study 17. Abnormal laboratory values Grade 2 or higher as defined in CTCAE v4.03 for GGT, total bilirubin (except in subjects diagnosed with Gilbert's syndrome), creatinine, hemoglobin, WBC count, platelet count, PT and aPTT 18. Female participant who is pregnant or demonstrates a positive urine or β-hCG result at screening assessment (if applicable) 19. Any vaccination with viral attenuated vaccines less than 30 days prior to the scheduled date of treatment (and use of prednisolone) 20. Previous treatment by Haematopoietic Stem Cell transplantation 21. Previous participation in a gene/cell therapy or ERT clinical trial 22. Participants who are anticipated to undergo a procedure involving anesthesia within 6 months post- drug administration 23. Dysphagia present at Grade 3 or higher, as defined in CTCAE v4.03
Study Treatment	Self-complementary adeno-associated virus serotype 9 carrying the human *SGSH* gene under the control of a U1a promoter (scAAV9.U1a.hSGSH) will be 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.
Primary Outcome	• Product safety as defined by the incidence, type and severity of treatment-related adverse events and serious adverse events [Time frame: Month 1, 2, 3, 6, 12, 18, 24]. • Change from baseline in CSF heparan sulfate levels after treatment [Time frame: Month 1, 6, 12, 24] • Change from baseline in liver and/or spleen volumes after treatment, as measured by magnetic resonance imaging (MRI) [Time frame: Month 1, 6, 12, 24]
Secondary Outcomes	• Change from baseline in plasma or urine glycosaminoglycans or heparan sulfate after treatment [Time frame: Month 1, 6, 12, 18, 24]

	• Change from baseline in CSF or plasma or leukocyte SGSH enzyme activity levels after treatment [Time frame: Month 1, 6, 12, 24] • Change from baseline in brain volumes after treatment, as measured by MRI [Time frame: Month 12, 24] • Change from baseline in the Age Equivalent and Developmental Quotient (DQ) after treatment compared to Natural History Study data calculated by the Mullen Scales of Early Learning or the Kaufman Assessment Battery for Children; Second Edition, based on chronological and developmental age [Time frame: Month 6, 12, 18, 24] • Change from baseline in the Cognitive Age Equivalent and Developmental Quotient after treatment compared to Natural History Study, calculated using the Bayley Scales of Infant and Toddler Development – Third edition or the Kaufman Assessment Battery for Children. Second Edition, based on developmental age [Time Frame: Month 6, 12, 18, 24] • Change from baseline in the Adaptive Age Equivalent score after treatment compared to Natural History Study data, as assessed by parent report using the Vineland Adaptive Behavior Scale II Survey form [Time frame: Month 6, 12, 18, 24] • Change from baseline in sleep pattern as measured by the modified Children's Sleep Habits Questionnaire (CSHQ) [Time Frame: Month 6, 12, 18, 24] • Change from baseline in Pediatric Quality of Life Inventory (PedsQL™) Core Generic Scales total score [Time Frame: Month 6, 12, 18, 24] • Change from baseline in parent quality of life, using the Parenting Stress Index, 4th Edition (PSI-4) [Time Frame: Month 6, 12, 18, 24] • Change from baseline in gastrointestinal symptoms using the PedsQL™ Gastrointestinal Symptoms Scales [Time Frame: Month 6, 12 18, 24] • Parent Global Impression Score [Time Frame: Month 6, 12, 18, 24] • Clinical Global Impression Improvement Scale Score [Time Frame: Month 6, 12, 18, 24] • Change from baseline in Parent Symptoms Score Questionnaire [Time Frame: Month 6, 12, 18, 24] • Change from baseline in Body Mass Index after treatment [Time Frame: Month 6, 12, 18, 24] • Incidence and change from baseline in abnormalities in standard awake 45-minutes- EEG monitoring [Time frame: Month 6, 12, 18, 24] • Determination of vector shedding analysis in plasma, saliva, urine and feces will provide preliminary data for the Environmental Risk Assessment (ERA)

Exploratory Outcomes	• CCI • CCI • CCI
Study Duration	Participants will be tested at baseline and return for follow up visits on Days 7, 14, 30, 60, 90, 180, and at 12, 18, and 24 Months for active monitoring.
Sample Size	This is an open label study in up to 12 participants with middle and advanced phase of MPS IIIA. Participants will receive a single intravascular infusion at a dose of 3 x 10^{13} vg/kg.
Statistical Analysis	This is a Phase I/II trial with safety and efficacy (change in CSF heparan sulfate levels and liver volume after treatment) as the primary outcomes. Secondary outcomes include additional efficacy measures several of which are exploratory. These include changes in heparan sulfate and/or total GAGs in plasma/urine, changes in SGSH enzymatic activity in CSF/leukocytes/plasma, changes in liver and brain volumes, changes in cognitive and behavioural measures, and changes in quality of life, sleep or seizures. Data of post-gene transfer monitoring will be compared with baseline data and a set of natural history data using the appropriate statistical analysis. A final Statistical Analysis Plan will be prepared before the database lock, including a stratification of participants based on Age Equivalent scores above or below 18 months. This SAP will include an interim analysis to be conducted when all participants have reached Month 12 follow-up.
Long-term follow-up	After the 24-month visit, participants will be requested to participate in a long term follow up study (LTFU-ABO-102, EudraCT number 2019- 002979-34) consisting of monitoring for a minimum of 3 years for a total period of five years posttreatment.

TABLE OF CONTENTS

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLES....2
1. PROTOCOL SYNOPSIS....5
TABLE OF CONTENTS....9
SCHEDULE OF EVALUATIONS....12
2. LIST OF ABBREVIATIONS....17
3. INTRODUCTION....20
3.1. Background....20
3.2. Nonclinical Studies....20
3.3. Clinical Program....21
4. STUDY DESIGN....23
4.1. Study Population....23
4.2. Inclusion/Exclusion Criteria....23
4.2.1. Inclusion Criteria....23
4.2.2. Exclusion Criteria....23
4.3. Dosing Plan....25
4.4. Prior and Concomitant Therapy....25
4.4.1. Prohibited Medications....25
5. STUDY PROCEDURES....26
5.1. Schedule of Evaluations....26
5.2. Clinical Trial Documentation....26
5.3. Screening and Enrollment....26
5.3.1. Screening Visits 1 and 2 (Day -45 through Day -1)....26
5.3.2. Pre-Infusion Visit (Day -1)....30
5.4. Gene Transfer....31
5.4.1 Day of Gene Transfer (Day 0)....31
5.5. Post Gene Transfer Monitoring Plan....33
5.5.1. Up to 48-Hours Inpatient Monitoring (Days 1 and 2)....33
5.5.1.1. Day 1....33
5.5.1.2. Day 2....35
5.5.2. Post-Gene Transfer Monitoring (Days 7, 14, 30)....35
5.5.2.1. Day 7 (+/- 2 days)....35

5.5.2.2. Day 14 (+/- 2 days) 36
5.5.2.3. Day 30 (+/- 3 days) 37
5.5.2.4. 5.5.2.4 Day 45 (+/- 3 days) 38
5.5.2.5. Day 60 (+/- 7 days) 38
5.5.2.6. Day 75 (+/- 3 days) 39
5.5.2.7. Day 90 (+/- 7 days) 39
5.5.2.8. Two Weeks Post Steroids Taper (+/- 7 days) 40
5.5.2.9. Day 120 (+/- 7 days) and Day 150 (+/- 7 days) 40
5.5.2.10. Day 180 (+/- 21 days) 40
5.5.2.11. Month 12 (+/- 30 days) 43
5.5.2.12. Month 18 (+/- 30 days) 45
5.5.2.13. Month 24 (+/- 30 days) 47
5.6. Long-Term Monitoring 49
5.7. Outcome Measures 49
6. SAFETY 52
6.1. Definitions 52
6.1.1. Adverse Event (AE) and Adverse Reaction (AR) 52
6.1.2. Serious Adverse Event (SAE) and Serious Adverse Reaction (SAR) 53
6.1.3. Suspected Unexpected Serious Adverse Reaction (SUSAR) 54
6.2. Assessment of Severity (Intensity) 54
6.2.1. Grade 1 54
6.2.2. Grade 2 54
6.2.3. Grade 3 54
6.2.4. Grade 4 54
6.2.5. Grade 5 54
6.3. Assessment of Causality 54
6.4. Recording 55
6.5. Reporting of SAEs and SARs 56
6.6. Reporting of pregnancy 58
7. DOSING NEW PARTICIPANTS AND STOPPING/DISCONTINUATION RULES 59
7.1. Dose New Participants 59
7.2. Stopping/Discontinuation Rules 59

8. ETHICAL AND REGULATORY ASPECTS 60
8.1. Ethical Review Board 60
8.2. Informed Consent 60
8.3. Confidentiality Information 61
8.4. Compensation for Participants 61
8.5. Insurance Policy 61
8.6. Notifications to Health Authorities 62
9. STUDY REPORTS 63
9.1. Final Study Report 63
9.2. Annual Study Reports 63
9.3. Data Safety Monitoring Plan 63
9.3.1. The Data Safety Monitoring Board 63
9.3.2. DSMB Reporting and Meetings 64
9.3.3. Membership 64
9.4. Clinical Monitoring of the Study 64
9.4.1. Data Management and Study Forms 64
10. SAMPLE MANAGEMENT 66
11. GMO RISK MANAGEMENT 67
12. REFERENCES 70
STATEMENT OF COMPLIANCE 72

SCHEDULE OF EVALUATIONS

STUDY TIMELINE OF EVENTS																				
Study Interval	**Screening**		**Pre Infusion Visit**	**Hospital Admission/ Vector Injection (Inpatient)**	**Inpatient**		**Follow-Up (Outpatient)**													
Visit #	**Visit 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 +/- 2 days**	**Day 14 +/- 2 days**	**Day 30 +/- 3 days**	**Day 45 +/- 3 days**	**Day 60 +/- 7 days**	**Day 75 +/- 3 days**	**Day 90 +/- 7 days**	**2 weeks post steroids +/- 7 days**	**Day 120 +/- 7 days**	**Day 150 +/- 7 days**	**Day 180 +/- 21 days**	**Month 12 +/- 30 days**	**Month 18 +/- 30 days**	**Month 24 +/- 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
CCI	X			-													X	X	X	X
CCI 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]

STUDY TIMELINE OF EVENTS																				
Study Interval	**Screening**		**Pre Infusion Visit**	**Hospital Admission/ Vector Injection (Inpatient)**	**Inpatient**		**Follow-Up (Outpatient)**													
Visit #	**Visit 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 +/- 2 days**	**Day 14 +/- 2 days**	**Day 30 +/- 3 days**	**Day 45 +/- 3 days**	**Day 60 +/- 7 days**	**Day 75 +/- 3 days**	**Day 90 +/- 7 days**	**2 weeks post steroids +/- 7 days**	**Day 120 +/- 7 days**	**Day 150 +/- 7 days**	**Day 180 +/- 21 days**	**Month 12 +/- 30 days**	**Month 18 +/- 30 days**	**Month 24 +/- 30 days**
CCI		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
CCI 25m walk	X																X	X	X	X
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	X

STUDY TIMELINE OF EVENTS																				
Study Interval	**Screening**		**Pre Infusion Visit**	**Hospital Admission/ Vector Injection (Inpatient)**	**Inpatient**		**Follow-Up (Outpatient)**													
Visit #	**Visit 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**
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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 sequencing to confirm MPS IIIA diagnosis	X[8]																			
ELISpot	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	X	X
Plasma biobanking		X		X			X	X	X		X		X				X	X	X	X
CCI	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
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
CCI		X							X								X	X		X
CCI		X							X								X	X		X
CSF Biobanking		X							X								X	X		X
Brain MRI		X																X		X

STUDY TIMELINE OF EVENTS																				
Study Interval	**Screening**		**Pre Infusion Visit**	**Hospital Admission/ Vector Injection (Inpatient)**	**Inpatient**		**Follow-Up (Outpatient)**													
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CCI [redacted]		X																X		X
Abdominal MRI		X							X								X	X		X
CCI [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.
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. CCI 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, CCI PSI-4, PedsQL, and CSHQ if applicable.
14. CCI
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.
18. CCI
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.

2. LIST OF ABBREVIATIONS

'suspected' SARs	'suspected' serious adverse reactions
°C	degrees Celsius
AAV9	associated virus serotype 9
CCI	[redacted]
ACDP	Advisory Committee on Dangerous Pathogens
AE	adverse event
ALT	alanine transaminase
AR	ADVERSE REACTION
AST	Aspartate aminotransferase
BBB	blood-brain barrier
BUN	Blood urea nitrogen
CBC	Complete blood cell count
CFR	Code of Federal Regulations
CNS	central nervous system
CRF	Case Report Forms
CRO	Contract Research Organization
CSF	Cerebral spinal fluid
CSHQ	Children's Sleep Habits Questionnaire
CTCAE	Common Terminology Criteria for Adverse Events v4.03
DNA	deoxyribonucleic acid
DQ	Development Quotient
DSMB	Data Safety Monitoring Board
DSUR	Development safety update report
EC	European Commission
ECG	electrocardiogram
ECHO	echocardiogram
EDC	electronic data capture
EEG	Electroencephalogram
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ERT	enzyme replacement therapy
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials

F	bioavailability
FCI	*Fluid-Crystalized Index*
g	gram
GAG	glycosaminoglycan
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice
GMO	genetically modified organism
hSGSH	human N-sulfoglucosamine sulfohydrolase
IB	Investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IND	Investigational New Drug (application)
INR	international normalized ratio
IRB	Institutional Review Board
IV	intravenous
kg	kilogram
L	liter/litre(s)
LP	Lumbar puncture
m	meter
min	minute(s)
mL	milliliter(s)
MPS	Mucopolysaccharidosis
MRI	magnetic resonance imaging
NCH	Nationwide Children's Hospital
NOAEL	no-observable-adverse-effect-level
CCI	[redacted]
PedsQL	Pediatric Quality of Life Inventory™
PICFs	Patient Informed Consent Forms
PSI-4	Parenting Stress Index, 4th Edition
PT	prothrombin time
PTT	partial thromboplastin time
RH	relative humidity
RSI	Reference Safety Information
SAE	serious adverse event
SAP	Statistical Analysis Plan

SAR	SERIOUS ADVERSE REACTION
CCI	[redacted]
serum/plasma GGT	serum/plasma gamma-glutamyl transpeptidase
SGSH	sulfoglucosamine sulfohydrolase
SMP	Safety Management Plan
SUSAR	SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION
Ultragenyx	Ultragenyx Pharmaceutical Inc.
USA	United States of America
UV	ultraviolet
WBC	White blood cell
WHO	World Health Organisation
WMA	World Medical Association

3. INTRODUCTION

3.1. Background

MPS IIIA is a devastating lysosomal storage disease, caused by a single gene defect (Neufeld and Cantz, 1971; Neufeld and Muezner, 2014; Weber et al., 1999). Somatic manifestations of MPS IIIA occur in all patients and can vary compared to other MPS disorders. Infants with MPS IIIA may demonstrate normal development at birth. However, the disease is relentlessly progressive, with deterioration of social and adaptive abilities, neurocognitive decline, and premature death. It can be divided into three phases (Wijburg et al., 2013). In the first phase, after 1-2 years of normal development, developmental delay (speech/language delays) and somatic changes (mild coarsening of facial features, frequent otitis media and hearing loss, hepatomegaly, mild dysostosis multiplex) become apparent between ages 1 and 4 years. In the second phase, which typically presents around ages 3-4 years, neurological manifestations become apparent, including severe behavioral problems, regression of skills and progressive mental deterioration. In the final phase, behavioral problems slowly disappear but cognitive decline progresses to a vegetative state with spasticity, seizures and swallowing problems. In MPS IIIA, approximately 70% of children die from complications of the disease prior to reaching their 18th birthday (USA MPS Society and Greenwood labs, unpublished data available on request).

Quite importantly, there is no treatment currently available for the disease (de Ruijter et al., 2011). AAV-mediated gene transfer to restore SGSH activity has emerged as a therapeutic strategy with great potential for MPS IIIA patients.

3.2. Nonclinical Studies

CCI

CCI [redacted]

Our ABO-102 gene transfer findings are well positioned to move forward to test in a clinical gene transfer trial for patients with MPSIIIA. To date, a single IV administration of scAAV9.U1a.hSGSH has been well tolerated in an ongoing clinical study, ABT-001 (NCT02716246).

3.3. Clinical Program

An observational study in MPS IIIA and MPS IIIB patients was conducted at Nationwide Children's Hospital (NCH) (Columbus, OH) prior to the initiation of the ABO-102 program. This study enrolled 15 participants with MPS IIIA and 10 participants with MPS IIIB (Truxal et al., 2016).CCI [redacted]

CCI [redacted]

CCI

This proposed Phase I/II study is designed to assess the safety and clinical response to the restoration of N-sulfoglucosamine sulfohydrolase (SGSH) enzyme activity in the CNS and periphery following intravenous injection of a self-complementary adeno-associated vector (scAAV9) carrying the human SGSH transgene under the control of the U1a promoter. Based on pre-clinical studies, scAAV9 and the U1a promoter will permit the efficient long-term transgene expression and secretion of functional SGSH, with great potential for achieving clinical benefits in treating neurological, as well as somatic disorders, in MPS IIIA patients. The selected dose is based on the preclinical proof of concept data in the animal model as well as clinical safety data from the ongoing Phase I/II dose escalation study, ABT-001, which also utilizes ABO-102 administered by IV in a pediatric population. In the ABT-001 study, three (3) patients have been treated in Cohort 1 (5×10^{12} vg/kg), three (3) in Cohort 2 (1×10^{13} vg/kg) and eight (8) participants have been treated in the highest dose cohort at 3×10^{13} vg/kg with a favorable safety profile and no treatment-related SAEs reported through more than two years of follow-up in Cohort 1,and Cohort 2 and two years in several participants in Cohort 3.

The intravenous route of administration was selected based on nonclinical studies, and from the clinical perspective brings advantages based on the minimal participant intervention, avoiding safety complications associated with other administration routes (i.e., intrathecal, intracerebroventricular or intraparenchymal injections).

Several gene therapy studies using other transgenes and similar vectors have been conducted without significant adverse events. Clinical studies to date suggest that an immune response will be generated to AAV capsid proteins, but whether an immune response will develop against SGSH remains to be determined. Because the immune system of participants in this study will be exposed to two antigens upon infusion of the gene therapy vector, the AAV9 capsid (a foreign antigen) and the newly synthesized SGSH (a “self-antigen”), humoral and cellular immune responses against both antigens will be monitored.

Following transduction, CD8 T cells may be induced (or memory CD8 T cells be reactivated in participants exposed previously to AAV9) to eliminate transduced cells that express AAV protein-derived epitopes. Results from several clinical trials suggest that immunosuppression, for example with corticosteroids, may be necessary to control the development of a cellular immune response and achieve sustained expression of the enzyme. In the proposed clinical trial, participants will be treated with a short course of prednisolone (1 mg/kg/day from one day prior to the gene transfer to Day 60, with tapering over the ensuing 4-6 weeks).

4. STUDY DESIGN

This Phase I/II clinical trial is an open-label, single dose study of recombinant, self-complementary 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.

4.1. Study Population

The target population includes MPSIIIA participants with a 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.

Although highly unlikely due to the natural evolution of the disease, the clinical trial may potentially include female adolescents that would represent women of childbearing potential in a normal population, as defined in the Clinical Trial Facilitation Group document (HMA, 2014) (Buhrman et al., 2014) for clarification of effective contraception titled Recommendations Related to Contraception and Pregnancy Testing in Clinical Trials. MPS III participants with a severe phenotype in the middle and advanced phases of the disease would present with a very advanced cognitive decline. This means that the female adolescents with MPS III fitting these characteristics do not have sexual relationships and so, are highly unlikely to be in the position to get pregnant. There are no references of any progeny from MPS III patients, so the sponsor considers there is no need to use any additional contraception measures other than the "*de facto*" sexual abstinence. This should be a reliable contraceptive method during the entire period of risk associated with the study that represents the usual lifestyle of the participant. For safety reasons, pregnancy test will be performed on screening, infusion and all MRI/LP study visits; and pregnancy forms will be developed as part of the Safety Management Plan.

4.2. Inclusion/Exclusion Criteria

4.2.1. Inclusion Criteria

1. Diagnosis of MPS IIIA confirmed by the following methods:
    a. No detectable or significantly reduced SGSH enzyme activity by leukocyte assay, and
    b. Genomic DNA analysis demonstrating homozygous or compound heterozygous mutations in the SGSH gene
2. Cognitive Development Quotient (DQ) lower than 60 (calculated by Bayley Scales of Infant and Toddler Development - Third Edition)
3. Must be ambulatory, though may receive assistance with ambulation
4. Age range of 2 years up to 18 years (excluded).

4.2.2. Exclusion Criteria

1. Inability to participate in the clinical evaluation as determined by Principal Investigator

2. Identification of two nonsense or null variants on genetic testing of the SGSH gene
3. At least one S298P mutation in the SGSH gene
4. Has evidence of an attenuated phenotype of MPS IIIA
5. Presence of a concomitant medical condition that precludes lumbar puncture or use of anesthetics
6. Active viral infection based on clinical observations
7. Concomitant illness or requirement for chronic drug treatment that in the opinion of the PI creates unnecessary risks for gene transfer, or precludes the child from participating in the protocol assessments and follow-up
8. Participants with total anti-AAV9 antibody titers ≥ 1:100 as determined by ELISA binding immunoassay
9. Participants with a positive response for the ELISPOT for T-cell responses to AAV9
10. Serology consistent with exposure to HIV, or serology consistent with active hepatitis B or C infection
11. Bleeding disorder or any other medical condition or circumstance in which a lumbar puncture (for collection of CSF) is contraindicated according to local institutional policy
12. Visual or hearing impairment sufficient to preclude cooperation with neurodevelopmental testing
13. Any item (braces, etc.) which would exclude the participant from being able to undergo MRI according to local institutional policy
14. Any other situation that precludes the participant from undergoing procedures required in this study
15. Participants with cardiomyopathy or significant congenital heart abnormalities
16. The presence of significant non-MPS IlIA related CNS impairment or behavioral disturbances that would confound the scientific rigor or interpretation of results of the study
17. Abnormal laboratory values Grade 2 or higher as defined in CTCAE v4.03 for GGT, total bilirubin (except in subjects diagnosed with Gilbert's syndrome), creatinine, hemoglobin, WBC count, platelet count, PT and aPTT
18. Female participant who is pregnant or demonstrates a positive urine or βhCG result at screening assessment (if applicable).
19. Any vaccination with viral-attenuated vaccines less than 30 days prior to the scheduled date of treatment (and use of prednisolone)
20. Previous treatment by Haematopoietic Stem Cell transplantation
21. Previous participation in a gene/cell therapy or ERT clinical trial.
22. Participants who are anticipated to undergo a procedure involving anesthesia within 6 months post- drug administration

23. Dysphagia present at Grade 3 or higher, as defined in CTCAE v4.03

NOTE: Potential participants with abnormal laboratory values may be re-screened for specific laboratory tests within the screening period (the 45 days prior to dosing) before being designated a screen failure. Repeat values within the normal range will be acceptable for inclusion.

4.3. Dosing Plan

This is a single dose open-label clinical trial. All participants will receive 3 x 10^{13} vg/kg of ABO-102 delivered one time through a venous catheter inserted into a peripheral limb vein.

4.4. Prior and Concomitant Therapy

All medicinal products that are already being prescribed to participants as common routine care will be continued during the clinical trial, with the exception of the prohibited medications listed in Section 4.4.1.

Any concomitant medications administered or discontinued during the study should be recorded on the eCRF.

In the event of an emergency, any needed medications may be prescribed without prior approval, but the medical monitor must be notified of the use of any excluded medications immediately thereafter.

4.4.1. Prohibited Medications

Any immune modifying medication other than the prescribed oral prednisolone (other than use of inhaled corticosteroids to manage chronic respiratory conditions) is prohibited.

5. STUDY PROCEDURES

5.1. Schedule of Evaluations

This clinical trial protocol is based in large part on observations from MPS IIIA and MPS IIIB participants enrolled in the observational study previously described, and the ABT-001 clinical trial which is currently ongoing (NCT02716246, EudraCT number 2015-003904-21). Additionally, according to local regulatory requirements, a plan for vector shedding in blood and other body fluids is included as part of an environmental risk assessment.

For a general overview of the procedure and visits, please see the Schedule of Evaluations.

5.2. Clinical Trial Documentation

All the information regarding study IMP request, shipment, storage, management and destruction is described in the study specific Pharmacy Manual.

The procedures that describe the collection, processing, labelling, storage, and shipment for the study samples are described in the Laboratory Manual. The study samples have been scheduled to allow a maximum blood volume of 35 ml per study visit, providing flexibility to the sites to reduce volume as per site policy if needed. Additional adhoc analysis on blood samples collected at any particular visit may be performed at the discretion of the PI.

5.3. Screening and Enrollment

5.3.1. Screening Visits 1 and 2 (Day -45 through Day -1)

The screening evaluations will take place over two visits (preferentially two weeks apart) to allow time for ELISA and ELISPOT results to be available before the participant undergoes sedation/anesthesia and other invasive clinical assessments, as the former tests present a significant chance of being exclusionary and the latter assessments puts the children under additional risks and therefore should not be conducted unless the probabilities to be enrolled in the trial are high.

Each screening visit may take place over multiple consecutive days if deemed necessary by the Principal Investigator to accommodate all the clinical assessments that need to be performed.

The following evaluations will be conducted during Screening Visit 1:

- Informed consent process
- Demographics (including age, gender, race, and date of birth)
- Medical history (general and MPS related)
- A complete physical examination with a head circumference measurement
- Adverse events (upon ICF signature)
- Concomitant medications
- Vital signs (temperature, respiratory rate, heart rate, blood pressure)

- Height and weight
- The participant will be CCI walking a 25-meter distance
- CCI
- Echocardiogram
- ECG
- Lab work will include:
  - Complete blood cell count (CBC) and differential
  - Electrolytes
  - Serum/plasma total protein
  - Albumin
  - Prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR)
  - Creatinine/Blood urea nitrogen (BUN)
  - Aspartate aminotransferase (AST), alanine transaminase (ALT), serum/plasma gamma-glutamyl transpeptidase (serum/plasma GGT)
  - Alkaline phosphatase
  - Amylase
  - Serum/plasma total bilirubin
  - Random glucose
  - Troponin
  - Plasma and leukocyte SGSH enzyme activity levels
  - Plasma heparan sulfate levels
  - CCI
  - Urine GAG and heparan sulfate levels
  - Urinalysis
  - Urine or Serum pregnancy test (if applicable)
- Samples for vector shedding (urine, saliva and feces)
- ELISpots for T-cell responses to AAV9 and SGSH
- ELISA for detection of total antibodies to AAV9 and antibodies to SGSH
- CCI
- Confirm diagnosis of MPS IIIA via gene sequencing (if not previously done)
- Cognitive function and adaptive functioning assessment using:

- Neurocognitive validity form (initial set up for first scales)
- Vineland Adaptive Behavior Scale II- Survey form, parental rating of adaptive functioning
- Bayley Scales of Infant and Toddler Development – Version III - Cognitive, Language and Motor. If children obtain a developmental age older than 36 months with the Bayley, the Kaufman Assessment Battery for Children, Second Edition, will be used also and will replace the Bayley Scales in the next visits
- Pediatric Quality of Life Inventory (PedsQL™) Core Generic Scales for parents
- Pediatric Quality of Life Inventory PedsQL™ Gastrointestinal Symptoms Scales for parents

The neurocognitive evaluations at this visit and along all other visits during the study will be CCI *to allow for the possibility of future auditing by an external psychologist.*

The Vineland Adaptive Behaviour scale will always be the first cognitive/adaptive functioning scale to be used in all visits, to obtain an estimate of the child's developmental level that will help for following evaluations.

The KABC-II subtests required for the Fluid-Crystalized Index (FCI) will be administered. After the FCI is completed, the subtests required for the Nonverbal Index will be administered if the child is able to continue with the testing session.

The rater/s and parent participating on the evaluation should be consistently the same during the trial for each participant as much as possible. These assessments may be performed locally with an external rater, if the family signed the consent annex and there is a qualified rater trained for the study procedures.

- Modified Children's Sleep Habits Questionnaire (CSHQ)
- Parent Symptom Score Questionnaire, to collect list of symptoms and associated ranking.

Vector shedding samples for urine, feces and saliva are collected at Screening Visit 1. In the event that urine, saliva and/or feces samples are unable to be obtained at Screening Visit 1, they will be obtained at Screening Visit 2.

The following evaluations will be conducted during Screening Visit 2:

- Weight
  - The weight obtained at Screening Visit 2 will be used to calculate the viral vector dose
- Adverse events
- Concomitant medications

- CCI [redacted]
- Cognitive function and adaptive functioning assessment using:
  - Neurocognitive validity form (final set up for following scales)
  - Mullen Scales of Early Learning, both non-verbal assessments of cognitive function. If children obtain a developmental age older than 60 months with the Mullen, the Kaufman Assessment Battery for Children, Second Edition, will be used also and will replace the Mullen Scales in the next visits
  - CCI [redacted]
  - Parenting Stress Index, 4th Edition (PSI-4) short form
- Plasma and leukocyte SGSH enzyme activity levels
- Plasma heparan sulfate levels
- CCI [redacted]
- Abdominal MRI to measure liver and spleen volumes
- 45-min EEG
- Lumbar puncture (LP) will be performed
  - CSF analysis
    - SGSH enzyme activity
    - heparan sulfate levels
    - CCI [redacted]
    - protein, glucose, cell count and differential
    - CCI [redacted]
    - CSF biobanking
- Labs will be obtained, including:
  - Alpha-fetoprotein
  - Hepatitis (B, C) and HIV
  - Plasma biobanking
- Samples for vector shedding (plasma)
- The MRI and LP, CCI [redacted] will be performed while the participant is under a single sedation/anesthesia event under the direction of a qualified anesthesiologist. The same apply to other visits throughout the protocol.
- Vector shedding samples for plasma will be taken at Screening Visit 2. In the event that urine, saliva and/or feces samples are unable to be obtained at Screening Visit 1, they will be obtained at Screening Visit 2.

Scale	Development Age				Assessment performed by
	6-24 months	24-42 months	42-68 months	Above 68 months	
Vineland Adaptive Behavior Scale II- Survey form	X	X	X	X	Rater
CCI	X	X	X	X	Caregiver
Mullen Scales of Early Learning	X	X	X*		Rater
Bayley Scales of Infant and Toddler Development – Version III- Cognitive, Language and Motor	X	X			Rater
Kaufman Assessment Battery for Children, Second Edition			X*	X	Rater
PedsQL™ Core Generic Scales	X	X	X	X	Caregiver
PedsQL™ Gastrointestinal Symptoms Scales	X	X	X	X	Caregiver
PSI-4	X	X	X	X	Caregiver
CSHQ	X	X	X	X	Caregiver
Parent Global Impression Score	X	X	X	X	Caregiver
Clinical Global Impression Improvement Scale	X	X	X	X	Principal Investigator
Parent Symptom Score Questionnaire	X	X	X	X	Caregiver
Total number of scales	**11**	**11**	**11**	**10**	

* At least one assessment done in parallel for both scales to ensure a correct transition.

5.3.2. Pre-Infusion Visit (Day -1)

Participants enrolled based on the screening data will arrive to the hospital within 24 hours prior to gene transfer.

They will undergo the following evaluations:

- Adverse events
- Physical Examination
- Vital signs (temperature, respiratory rate, heart rate, blood pressure)
  - Weight
- Concomitant medications
- Prophylactic enteral prednisone or prednisolone will be started
- Labs will be obtained, including
  - CBC and differential
  - Electrolytes
  - Serum/plasma total protein

- Albumin
- PT, PTT, INR
- Creatinine/BUN
- AST, ALT, serum/plasma GGT
- Alkaline phosphatase
- Amylase
- Serum/plasma total bilirubin
- Random glucose
- Troponin

In previous gene therapy studies, antigen-specific T-cell response to the AAV9 vector have been reported (Mingozzi and High, 2011). This is an expected response between 2 - 12 weeks following gene transfer. One possible consequence of such antigen-specific T-cell responses is clearance of the transduced cells and loss of transgene expression.

In order to reduce the risk of the host immune response to our AAV9-based therapy, participants will be started on prophylactic enteral prednisone or prednisolone (glucocorticoid) (approximately 1 mg/kg/day) one day prior to the gene transfer and only after passing all inclusion and exclusion criteria (in the event that a measure is repeated on Day -1). This will be continued after gene transfer as discussed in Section 5.5.1.

Prophylactic enteral prednisone or prednisolone will not be provided by the Sponsor; the standard of care at the site/country should be used for prophylaxis.

5.4. Gene Transfer

5.4.1 Day of Gene Transfer (Day 0)

Participants will be admitted to the hospital on the day of gene transfer (Day 0) and transferred to an independent hospital room after the gene transfer.

On the day of gene transfer (Day 0) prior to vector infusion, the participant will undergo the following evaluations:

- Adverse events
- Concomitant medications
- Vital signs (temperature, heart rate, respiratory rate, blood pressure, pulse oximetry)
- A CCI will be taken of the chosen injection site prior to and after vector administration (approximately 4 hours after treatment end)
- Labs including:
  - Plasma biobanking
  - Urine pregnancy test (if applicable)

- Samples for vector shedding (plasma, urine, saliva and feces) at approximately 4 and 8 hours after completion of gene transfer

An independent assessment will be performed by sedation/anesthesia staff per local procedures with vitals collected for clinical purposes to ensure the participant is cleared for gene transfer.

If the participant appears inadequately hydrated in the judgment of the Principal Investigator, bolus(es) of 10-20 mL/kg normal saline may be given during the time between participant check-in and gene transfer. Participants will be continued on their usual diet until eight hours prior to gene transfer, after which they will have no solid food; clear liquids will be allowed up until two hours prior to gene transfer, after which they will be fully NPO. They will resume their usual diet after they have returned to pre-sedation/anesthesia baseline.

Gene transfer will be performed under sterile conditions in an appropriate in-patient facility, under light to moderate sedation/anesthesia if considered necessary by the clinical investigator, under the direction of a qualified anesthesiologist / intensivist. The specific approach may vary, but the participant may be sedated using inhaled nitrous prior to induction with propofol via an IV and maintained with inhaled sevoflurane or a propofol drip. Sedation/anesthesia is being utilized in this instance due to the frequently hyperactive and uncooperative behavior of the participants, along with the undefined safety of this biologic study agent, and with an aim of maximizing potential study participation benefit to the pediatric participant by preventing study agent subcutaneous infiltration or IV loss with study agent spillage. In those participants who in the opinion of the Principal Investigator (and in consultation with the anesthesiologist/intensivist and parents) are determined to not need sedation/anesthesia in order to safely deliver the vector, sedation/anesthesia may be deferred.

All participants in this trial will receive an intravenous injection of ABO-102 via peripheral limb vein at a dose of 3.0×10^{13} vg/kg.

The vector request, shipment, storage, preparation and management are described in the Pharmacy Manual. Site should keep records of Investigational Product and prednisone/ prednisolone medication accountability.

Each vector dose will be given undiluted from syringes determined to be compatible with the vector and, prepared by the Investigational/Research Drug Pharmacy. Infusion will be performed using an infusion pump compatible with the supplied infusion kits. At the estimated vector product concentration of 1×10^{13} vg/mL, this would equate to 3 mL/kg. The vector salt solution is expected to be approximately 400 mOsmol/L.

The infusion rate will not be slower than the slowest rate at which the infusion set up compatibility testing was done. The infusion rate will not approach or exceed 2 mL/kg/min (a rapid bolus rate) for any pediatric participant. The infusion will be given over approximately 15 to 45 minutes, incorporating competing concerns including maximizing uptake across the blood-brain barrier and limiting sedation/anesthesia time versus limiting risk for IV infiltration and infusing slowly enough to observe for evidence of infusion reaction before entire dose is given. Depending on vector lot concentration and other factors, infusion rate is expected to be around 0.03-0.08 mL/kg/min. The vector will be flushed from the infusion tubing using 20 mL Lactated Ringer's/Hartmann's.

Participants will be closely monitored for side effects during the infusion, including continuous heart rate, respiratory rate, and pulse oximetry; and intermittent blood pressure monitoring. Heart rate, respiratory rate, pulse oximetry, temperature, and blood pressure will be measured before and immediately after the infusion. Monitoring will be repeated at:

- 15 minutes post-infusion
- 1 hour post-infusion (window ± 15 minutes)
- 2 hours post-infusion (window ± 15 minutes)
- 4 hours post-infusion (window ± 60 minutes)
- 8 hours post-infusion (window ± 2 hours)
- 12 hours post-infusion (window ± 3 hours)
- 24 hours post-infusion (window ± 3 hours)
- 48 hours post-infusion (window ± 3 hours)

Infusion reactions: Infusion will be terminated for evidence of an allergic reaction of **Grade 2 or greater**, including anaphylaxis (based upon CTCAE v4.03 criteria) and reported using these criteria:

Grade 1: Transient flushing or rash, drug fever <38 degrees C (<100.4 degrees F); intervention not indicated

Grade 2: Rash, flushing, urticaria, dyspnea, drug fever >38°C:

Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics); prophylactic medications indicated for ≤24 hrs

Grade 3: Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)

Grade 4: Life-threatening consequences; urgent intervention indicated Grade 5: Death

Under CTCAE v4.03 criteria, **anaphylaxis** is by definition a Grade 3 (Symptomatic bronchospasm with or without urticaria; allergy-related edema/angioedema, hypotension), and would result in infusion termination and systemic treatment.

Participants will remain in an independent hospital room following gene transfer and remain hospitalized for up to 48 hours post gene transfer.

5.5. Post Gene Transfer Monitoring Plan

5.5.1. Up to 48-Hours Inpatient Monitoring (Days 1 and 2)

The participant will see the Principal Investigator or designee on the morning of both Day 1 and Day 2 for the following evaluations:

5.5.1.1. Day 1

The following evaluations will be conducted at Day 1:

- Adverse events
- Concomitant medications
- Physical examination
- Vital signs (temperature, heart rate, respiratory rate, blood pressure, pulse oximetry)
- Labs will be obtained, including
  - CBC and differential
  - Electrolytes
  - Serum total protein
  - Albumin
  - PT, PTT, INR
  - Creatinine/BUN
  - AST, ALT, serum/plasma GGT
  - Alkaline phosphatase
  - Amylase
  - Serum/plasma total bilirubin
  - Random glucose
  - Troponin
  - Urinalysis
  - Plasma heparan sulfate levels.
  - CCI
  - Urine GAG and heparan sulfate levels
- Samples for vector shedding (plasma, urine, saliva and feces)
- A CCI will be taken of the injection site (approximately 24 h after infusion)

Oral prednisone or prednisolone administration will continue after the gene transfer itself and be tapered according to liver function testing and IFN-gamma T-cell studies (ELISpot assay) in the following weeks. If post-infusion IFN-gamma T-cell responses remain negative per the performing lab's criteria, the participant's prednisone or prednisolone dos will begin to be tapered around Day 60 post gene transfer. Tapering will proceed slowly, typically over 4 to 7 weeks. CCI Based on other studies, it is anticipated that oral prednisone or prednisolone administration should not exceed

120 days post gene transfer. Liver function testing (AST, ALT, GGT) will be repeated 2 weeks after the last dose of steroid. All prednisone or prednisolone administration and tapering details should be recorded in the EDC, including dose, start and end dates.

5.5.1.2. Day 2

The following evaluations will be conducted at Day 2:

- Adverse events
- Concomitant medications
- Physical examination
- Vital signs (temperature, heart rate, respiratory rate, blood pressure, pulse oximetry)
- Samples for vector shedding (plasma, urine, saliva and feces)

5.5.2. Post-Gene Transfer Monitoring (Days 7, 14, 30)

5.5.2.1. Day 7 (+/- 2 days)

The following evaluations will be conducted at Day 7:

- Medical history
- Adverse events
- Concomitant medications
- Physical examination
- Vital signs (temperature, heart rate, respiratory rate, blood pressure)
- Labs will be obtained, including
  - CBC and differential
  - Electrolytes
  - Serum/plasma total protein
  - Albumin
  - PT, PTT, INR
  - Creatinine/BUN
  - AST, ALT, serum/plasma GGT
  - Alkaline phosphatase
  - Amylase
  - Serum/plasma total bilirubin
  - Random glucose
  - Troponin

  - ELISA for detection of total antibodies to AAV9 and antibodies to SGSH
  - Plasma and leukocyte SGSH enzyme activity levels
  - Plasma heparan sulfate levels
  - CCI
  - Urine GAG and heparan sulfate levels
  - Urinalysis
  - Plasma biobanking
- Samples for vector shedding (plasma, urine, saliva and feces)

5.5.2.2. Day 14 (+/- 2 days)

The following evaluations will be conducted at Day 14:

- Medical history
- Adverse events
- Concomitant medications
- Physical examination
- Vital signs (temperature, heart rate, respiratory rate, blood pressure)
- Labs will be obtained, including
  - CBC and differential
  - Electrolytes
  - Serum/plasma total protein
  - Albumin
  - PT, PTT, INR
  - Creatinine/BUN
  - AST, ALT, serum/plasma GGT
  - Alkaline phosphatase
  - Amylase
  - Serum/plasma total bilirubin
  - Random glucose
  - Troponin
  - ELISA for detection of total antibodies to AAV9 and antibodies to SGSH
  - Plasma and leukocyte SGSH enzyme activity levels
  - Plasma heparan sulfate levels.

  - CCI [redacted]
  - Urine GAG and heparan sulfate levels
  - Urinalysis
  - ELISpots for T-cell responses to AAV9 and SGSH
  - Plasma biobanking
- Samples for vector shedding (plasma, urine, saliva and feces)

5.5.2.3. Day 30 (+/- 3 days)

The following evaluations will be conducted at Day 30:

- Medical history
- Adverse events
- Concomitant medications
- Physical examination
- Vital signs (temperature, heart rate, respiratory rate, blood pressure)
- Height and weight
- Abdominal MRI to measure liver and spleen volumes
- Labs will be obtained, including
  - CBC and differential
  - Electrolytes
  - Serum/plasma total protein
  - Albumin
  - PT, PTT, INR
  - Creatinine/BUN
  - AST, ALT, serum/plasma GGT
  - Alkaline phosphatase
  - Amylase
  - Serum/plasma total bilirubin
  - Random glucose
  - Troponin
  - Plasma and leukocyte SGSH enzyme activity levels
  - Plasma heparan sulfate levels
  - Urine GAG and heparan sulfate levels

- Urinalysis
- ELISpots for T-cell responses to AAV9 and SGSH
- ELISA for detection of total antibodies to AAV9 and antibodies to SGSH
- CCI
- Plasma biobanking

- Lumbar puncture (LP) will be performed under sedation/anesthesia
  - CSF analysis
    - SGSH enzyme activity
    - heparan sulfate levels
    - CCI
    - Protein, glucose, cell count and differential
    - CCI
    - CSF biobanking
- Samples for vector shedding (plasma, urine, saliva and feces)

If an elevation in amylase levels is observed after gene transfer and has not returned to baseline values by Day 30, amylase will continue to be analyzed in further visits until levels return to baseline values. Those analyses will include lab collections performed at home if the participant is unable to travel to the hospital.

5.5.2.4. 5.5.2.4 Day 45 (+/- 3 days)

Lab work at Day 45 will be done to evaluate safety. Participants unable to travel to the hospital will have their blood drawn by a contracted home care service.

The labs will evaluate:

- AST, ALT, serum/plasma GGT

5.5.2.5. Day 60 (+/- 7 days)

The following evaluations will be conducted at Day 60:

- Medical history
- Adverse events
- Concomitant medications
- Physical examination
- Vital signs (temperature, heart rate, respiratory rate, blood pressure)
- Weight
- Labs will be obtained, including: AST, ALT, serum/plasma GGT
- Plasma and leukocyte SGSH enzyme activity levels
- Plasma heparan sulfate levels

  - Troponin
  - Urine GAG and heparan sulfate levels
  - ELISpots for T-cell responses to AAV9 and SGSH
  - ELISA for detection of total antibodies to AAV9 and antibodies to SGSH
  - CCI
  - Plasma biobanking
  - Amylase (if applicable)
- Samples for vector shedding if applicable (plasma, urine, saliva and feces)

Vector shedding analysis post dosing, after Day 30, 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.

5.5.2.6. Day 75 (+/- 3 days)

Lab work at day 75 will be done to evaluate safety. Participants unable to travel to the hospital will have their blood drawn by a contracted home care service.

The labs will evaluate:

  - AST, ALT, serum/plasma GGT

5.5.2.7. Day 90 (+/- 7 days)

The following evaluations will be conducted at Day 90:

- Medical history
- Adverse events
- Concomitant medications
- Physical examination
- Vital signs (temperature, heart rate, respiratory rate, blood pressure)
- Weight
- Echocardiogram
- ECG
- Labs will be obtained, including
  - CBC and differential
  - Electrolytes
  - Serum/plasma total protein
  - Albumin
  - PT, PTT, INR

  - Creatinine/BUN
  - AST, ALT, serum/plasma GGT
  - Alkaline phosphatase
  - Alpha-fetoprotein
  - Amylase (if applicable)
  - Serum/plasma total bilirubin
  - Random glucose
  - Troponin
  - Plasma and leukocyte SGSH enzyme activity levels
  - Plasma heparan sulfate levels
  - Urine GAG and heparan sulfate levels
  - Urinalysis
  - ELISpots for T-cell responses to AAV9 and SGSH
  - ELISA for detection of total antibodies to AAV9 and antibodies to SGSH
  - Plasma biobanking
- Samples for vector shedding if applicable (plasma, urine, saliva and feces) (see instructions at Day 60)

5.5.2.8. Two Weeks Post Steroids Taper (+/- 7 days)

Participants unable to travel to the hospital will have their blood drawn by a contracted home care service.

The following labs will be conducted at a timepoint two weeks post last steroids dose and will evaluate:

- AST, ALT, serum/plasma GGT

5.5.2.9. Day 120 (+/- 7 days) and Day 150 (+/- 7 days)

Lab work at Days 120 and 150 will be done to evaluate safety. Participants unable to travel to the hospital will have their blood drawn by a contracted home care service.

The labs will evaluate:

- AST, ALT, serum/plasma GGT

5.5.2.10. Day 180 (+/- 21 days)

The following evaluations will be conducted at Day 180:

- Medical history
- Adverse events

- Concomitant medications
- Physical examination with a head circumference measurement
- Vital signs (temperature, heart rate, respiratory rate, blood pressure)
- Height and weight
- Neurocognitive validity form
- Cognitive function assessment using:
  - Vineland Adaptive Behavior Scale II-Survey form, parental rating of adaptive functioning
  - Mullen Scales of Early Learning, both non-verbal assessments of cognitive function. If children obtain a developmental age older than 60 months with the Mullen, the Kaufman Assessment Battery for Children, Second Edition, will also be used and will replace the Mullen Scales in the next visits
  - Bayley Scales of Infant and Toddler Development – Version III- Cognitive, Language and Motor. If children obtain a developmental age older than 36 months with the Bayley, the Kaufman Assessment Battery for Children, Second Edition, will also be used and will replace the Bayley Scales in the next visits
  - CCI
  - Parenting Stress Index, 4th Edition (PSI-4) short form
  - Pediatric Quality of Life Inventory (PedsQL™) Core Generic Scales for parents
    - Pediatric Quality of Life Inventory PedsQL™ Gastrointestinal Symptoms Scales for parents
- Modified Children's Sleep Habits Questionnaire (CSHQ) (This scale will be used if a sleep problem has been identified during the initial evaluation in Screening visit 1 or the medical history suggests there is a problem affecting child's sleep)
- Parent Global Impression Score
- Clinical Global Impression Improvement Scale
- Parent Symptom Score Questionnaire
- The participant will be CCI walking a 25-meter distance
- Abdominal MRI to measure liver and spleen volumes
- 45-min EEG
- CCI
- Echocardiogram
- ECG

- CCI [redacted]
- Labs will be performed including
  - CBC and differential
  - Electrolytes
  - Serum/plasma total protein
  - Albumin
  - PT, PTT, INR
  - Creatinine/BUN
  - AST, ALT, serum/plasma GGT
  - Alkaline phosphatase
  - Alpha-fetoprotein
  - Serum/plasma total bilirubin
  - Random glucose
  - Troponin
  - Plasma and leukocyte SGSH enzyme activity levels
  - Plasma heparan sulfate levels
  - CCI [redacted]
  - Urine GAG and heparan sulfate levels
  - Urinalysis
  - ELISpots for T-cell responses to AAV9 and SGSH
  - ELISA for detection of total antibodies to AAV9 and antibodies to SGSH
  - CCI [redacted]
  - Plasma biobanking
- Lumbar puncture (LP) will be performed under sedation/anesthesia
  - CSF analysis
    - SGSH enzyme activity
    - Heparan sulfate levels
    - CCI [redacted]
    - Protein, glucose, cell count and differential
    - CCI [redacted]

  - CSF biobanking

- Samples for vector shedding if applicable (plasma, urine, saliva and feces) (see instructions at Day 60)

This visit as well as those of Months 12, 18 and 24 will be conducted over two or more days to ensure that appropriate time is allocated for neurocognitive assessments, as well for caregiver-based evaluations. Breaks will be taken as needed for the family and the child.

5.5.2.11. Month 12 (+/- 30 days)

The following evaluations will be conducted at Month 12:

- Medical history
- Adverse events
- Concomitant medications
- Physical examination with a head circumference measurement
- Vital signs (temperature, heart rate, respiratory rate, blood pressure)
- Height and weight
- Neurocognitive validity form
- Cognitive function assessment using:
  - Vineland Adaptive Behavior Scale II-Survey form, parental rating of adaptive functioning
  - Mullen Scales of Early Learning, both non-verbal assessments of cognitive function. If children obtain a developmental age older than 60 months with the Mullen, the Kaufman Assessment Battery for Children, Second Edition, will be used also and will replace the Mullen Scales in the next visits
  - Bayley Scales of Infant and Toddler Development – Version III – Cognitive, Language and Motor. If children obtain a developmental age older than 36 months with the Bayley, the Kaufman Assessment Battery for Children, Second Edition, will be used also and will replace the Bayley Scales in the next visits
  - CCI [redacted]
  - Parenting Stress Index, 4th Edition (PSI-4) short form
  - Pediatric Quality of Life Inventory (PedsQL™) Core Generic Scales for parents
  - Pediatric Quality of Life Inventory PedsQL™ Gastrointestinal Symptoms Scales for parents
- Modified Children's Sleep Habits Questionnaire (CSHQ) (This scale will be used if a sleep problem has been identified during the initial evaluation in Screening visit 1 or the medical history suggest there is a problem affecting child's sleep)
- Parent Global Impression Score

- Clinical Global Impression Improvement Scale
- Parent Symptom Score Questionnaire
- The participant will be CCI walking a 25-meter distance
- CCI
- Abdominal MRI to measure liver and spleen volumes
- 45-min EEG
- CCI
- Echocardiogram
- ECG
- CCI
- Labs will be performed including:
  - CBC and differential
  - Electrolytes
  - Serum/plasma total protein
  - Albumin
  - PT, PTT, INR
  - Creatinine/BUN
  - AST, ALT, serum/plasma GGT
  - Alkaline phosphatase
  - Alpha-fetoprotein
  - Serum/plasma total bilirubin
  - Random glucose
  - Troponin
  - Plasma and leukocyte SGSH enzyme activity levels
  - Plasma heparan sulfate levels
  - CCI
  - Urine GAG and heparan sulfate levels
  - Urinalysis

  - ELISpots for T-cell responses to AAV9 and SGSH
  - ELISA for detection of total antibodies to AAV9 and antibodies to SGSH
  - CCI
  - Urine pregnancy test (if applicable)
  - Plasma biobanking
- Lumbar puncture (LP) will be performed under sedation/anesthesia
  - CSF analysis
    - SGSH enzyme activity
    - Heparan sulfate levels
    - CCI
    - Protein, glucose, and cell count and differential
    - CCI
    - CSF biobanking
- Samples for vector shedding if applicable (plasma, urine, saliva and feces) (see instructions at Day 60)

5.5.2.12. Month 18 (+/- 30 days)

The following evaluations will be conducted at Month 18:

- Medical history
- Adverse events
- Concomitant medications
- Physical examination with a head circumference measurement
- Vital signs (temperature, heart rate, respiratory rate, blood pressure)
  - Height and weight
- Neurocognitive validity form
- Cognitive function assessment using:
  - Vineland Adaptive Behavior Scale II-Survey form, parental rating of adaptive functioning
  - Mullen Scales of Early Learning, both non-verbal assessments of cognitive function. If children obtain a developmental age older than 60 months with the Mullen, the Kaufman Assessment Battery for Children, Second Edition, will also be used and will replace the Mullen Scales in the next visits
  - Bayley Scales of Infant and Toddler Development – Third edition- Cognitive, Language and Motor. If children obtain a developmental age older than 36 months with the Bayley, the Kaufman Assessment Battery for Children, Second Edition, will also be used and will replace the Bayley Scales in the next visits

  - CCI
  - Parenting Stress Index, 4th Edition (PSI-4) short form
  - Pediatric Quality of Life Inventory (PedsQL™) Core Generic Scales for parents
  - Pediatric Quality of Life Inventory PedsQL™ Gastrointestinal Symptoms Scales for parents
- Modified Children's Sleep Habits Questionnaire (CSHQ)This scale will be used if a sleep problem has been identified during the initial evaluation in Screening visit 1 or the medical history suggest there is a problem affecting child's sleep)
- Parent Global Impression Score
- Clinical Global Impression Improvement Scale
- Parent Symptom Score Questionnaire
- The participant will be CCI walking a 25-meter distance
- CCI
- 45-min EEG
- Labs will be performed, including
  - CBC and differential
  - Electrolytes
  - Serum/plasma total protein
  - Albumin
  - PT, PTT, INR
  - Creatinine/BUN
  - AST, ALT, serum/plasma GGT
  - Alkaline phosphatase
  - Alpha-fetoprotein
  - Serum/plasma total bilirubin
  - Random glucose
  - Troponin
  - Plasma and leukocyte SGSH enzyme activity levels
  - Plasma heparan sulfate levels
  - CCI
  - Urine GAG and heparan sulfate levels
  - Urinalysis

  - ELISpots for T-cell responses to AAV9 and SGSH
  - ELISA for detection of total antibodies to AAV9 and antibodies to SGSH
  - Plasma biobanking
- Samples for vector shedding if applicable (plasma, urine, saliva and feces) (see instructions at Day 60)

5.5.2.13. Month 24 (+/- 30 days)

The following evaluations will be conducted at Month 24:

- Medical history
- Adverse events
- Concomitant medications
- Physical examination with a head circumference measurement
- Vital signs (temperature, heart rate, respiratory rate, blood pressure)
- Height and weight
- Neurocognitive validity form
- Cognitive function assessment using:
  - Vineland Adaptive Behavior Scale II-Survey form, parental rating of adaptive functioning
  - Bayley Scales of Infant and Toddler Development – Third edition- Cognitive, Language and Motor. If children obtain a developmental age older than 36 months with the Bayley, the Kaufman Assessment Battery for Children, Second Edition, will also be used and will replace the Bayley Scales in the next visits
  - Mullen Scales of Early Learning, both non-verbal assessments of cognitive function. – Third edition. If children obtain a developmental age older than 60 months with the Bayley, the Kaufman Assessment Battery for Children, Second Edition, will also be used and will replace the Bayley Scales in the next visits
  - CCI
  - Parenting Stress Index, 4th Edition (PSI-4) short form
  - Pediatric Quality of Life Inventory (PedsQL™) Core Generic Scales for parents
  - Pediatric Quality of Life Inventory PedsQL™ Gastrointestinal Symptoms Scales for parents
- Modified Children's Sleep Habits Questionnaire (CSHQ) (This scale will be used if a sleep problem has been identified during the initial evaluation in Screening visit 1 or the medical history suggest there is a problem affecting child's sleep)
- Parent Global Impression Score

- Clinical Global Impression Improvement Scale
- Parent Symptom Score Questionnaire
- The participant will be CCI walking a 25-meter distance
- CCI
- Echocardiogram
- ECG
- CCI
- Labs will be performed including
  - CBC and differential
  - Electrolytes
  - Serum/plasma total protein
  - Albumin
  - PT, PTT, INR
  - Creatinine/BUN
  - AST, ALT, serum/plasma GGT
  - Alkaline phosphatase
  - Alpha-fetoprotein
  - Serum/plasma total bilirubin
  - Random glucose
  - Troponin
  - Plasma and leukocyte SGSH enzyme activity levels
  - Plasma heparan sulfate levels
  - CCI
  - Urine GAG and heparan sulfate levels
  - Urinalysis
  - ELISpots for T-cell responses to AAV9 and SGSH
  - ELISA for detection of total antibodies to AAV9 and antibodies to SGSH
  - CCI

  - Urine pregnancy test (if applicable)
  - Plasma biobanking
- CCI
- Abdominal MRI to measure liver and spleen volumes
- 45-min EEG
- Lumbar puncture (LP) will be performed under sedation/anesthesia
  - CSF analysis
    - SGSH enzyme activity
    - Heparan sulfate levels
    - CCI
    - Protein, glucose, cell count and differential
    - CCI
    - CSF biobanking
- Samples for vector shedding if applicable (plasma, urine, saliva and feces) (see instructions at Day 60)
- Participant Survey to assess the service providers for travelling, patient reimbursement, home nursing*

*This survey should also be assessed in the last visit of screening failures and withdrawal.

5.6. Long-Term Monitoring

The end of the clinical trial is defined as the Last Participant Last Visit. A participant is considered to have completed the study follow up period after completion of the 24-month visit.

When a participant has completed the 24-month study follow up for safety and efficacy, he or she will be requested to participate in a long-term follow-up study (LTFU-ABO-102, EudraCT number 2019-002979-34). During the long-term follow-up study participants will be followed for a minimum period of three years.

5.7. Outcome Measures

Due to the highly heterogenous population that will be enrolled in this trial and the degree of neurodegeneration associated with middle and advanced stages of MPS IIIA evolution, the possibilities that the treatment has a meaningful impact in the cognitive condition of the patients are very limited. For this reason we CCI selected the following primary outcome measures:

- Product safety as defined by the incidence, type and severity of treatment-related adverse events and serious adverse events [Time frame: Month 1, 2, 3, 6, 12, 18, 24]

- Change from baseline in CSF heparan sulfate levels after treatment [Time frame: Month 1, 6, 12, 24]
- Change from baseline in liver and/or spleen volumes after treatment, as measured by MRI [Time frame: Month 1, 6, 12, 24]

Cognitive evolution evaluation is proposed as secondary outcome, as well as adaptive functioning, biomarkers and biophysical changes and a series of potentially important assessment including sleep, quality of life of the child and the parents, gastrointestinal problems, body mass index or even other relevant symptoms identified by the parents in a Parent Symptom Score Questionnaire that will be used at screening and followed every 6 months. A list of secondary outcomes includes:

- Change from baseline in plasma or urine glycosaminoglycans or heparan sulfate after treatment [Time frame: Month 1, 6, 12, 18, 24]
- Change from baseline in CSF or plasma or leukocyte SGSH enzyme activity levels after treatment [Time frame: Month 1, 6, 12, 24]
- Change from baseline in brain volumes after treatment, as measured by MRI [Time frame: Month 12, 24]
- Change from baseline in the Age Equivalent and Developmental Quotient (DQ) after treatment compared to Natural History Study data calculated by the Mullen Scales of Early Learning or the Kaufman Assessment Battery for Children. Second Edition, based on chronological and developmental age [Time frame: Month 6, 12, 18, 24]
- Change from baseline in the Cognitive Age Equivalent and Developmental Quotient (DQ) after treatment compared to Natural History Study, calculated using the Bayley Scales of Infant and Toddler Development – Third edition or the Kaufman Assessment Battery for Children. Second Edition, based on developmental age [Time Frame: Month 6, 12, 18, 24]
- Change from baseline in the Adaptive Age Equivalent score after treatment compared to Natural History Study data, as assessed by parent report using the Vineland Adaptive Behavior Scale II Survey form [Time frame: Month 6, 12, 18, 24]
- Change from baseline in sleep pattern as measured by the CSHQ [Time Frame: Month 6, 12, 18, 24]
- Change from baseline in PedsQL™ Core Generic Scales score [Time Frame: Month 6, 12, 18, 24]
- Change from baseline in parent quality of life, using the PSI-4, 4th Edition [Time Frame: Month 6,12, 18, 24]
- Change from baseline in gastrointestinal symptoms using the PedsQL™ Gastrointestinal Symptoms Scales [Time Frame: Month 6,12, 18, 24]
- Parent Global Impression Score [Time Frame: Month 6,12, 18, 24]
- Clinical Global Impression Improvement Scale Score [Time Frame: Month 6, 12, 18, 24]

- Change from baseline in Parent Symptom Score Questionnaire [Time Frame: Month 6, 12, 18, 24]
- Change from Baseline in Body Mass Index after treatment [Time Frame: Month 6, 12, 18, 24]
- Incidence and change from baseline in abnormalities in standard awake 45-minute EEG monitoring [Time frame: Month 6, 12, 18, 24]
- Determination of vector shedding analysis in plasma, saliva, urine and feces will provide preliminary data for the Environmental Risk Assessment (ERA).

CCI

6. SAFETY

The Investigator or site staff is responsible for detecting, documenting and reporting events that meet the definition of an adverse event (AE) or a serious adverse event (SAE). All AEs (serious and not serious) occurring during the observation period established in this protocol must be documented. All adverse events will be followed until resolution or stabilization.

The study period during which adverse events must be reported is defined as the period from signature of the informed consent to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 24 months following the administration of study treatment and is considered the Final Visit for each participant. The Principal Investigator will adhere to any other SAE reporting requirements in accordance with national regulations, local laws, and the national institutional policies and procedures, as applicable. The Principal Investigator will be responsible for ensuring that the reporting requirements are fulfilled and will be held accountable for any reporting lapses.

It is important to note that for this clinical trial, Principal Investigators should only report the following AEs:

- All Grade 2 or greater AEs
- Grade 1 AEs considered by the Principal Investigator as clinically significant, independent of the association or relatedness to the study agent
- Grade 1 AEs assessed by the Principal Investigator as possibly, probably or definitely related to the study agent

Abnormal laboratory findings should be recorded as AEs when judged by the Principal Investigator/Sub-Investigator as clinically significant. Special attention should be considered for changes in AST/ALT, platelets and amylase.

There are no drug comparators used in this study, so there is only one Investigational Medicinal Product to assess the causality/expectedness evaluation, the gene therapy vector described in the Investigational Brochure.

6.1. Definitions

6.1.1. Adverse Event (AE) and Adverse Reaction (AR)

An AE is any untoward medical occurrence or unintended change (including physical, psychological, or behavioral) from the time ICF is signed, including inter-current illness, which occurs during the course of a clinical trial after treatment has started, whether considered related to treatment or not. 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 product, whether or not considered related to the medicinal product. Changes associated with normal growth and development that do not vary in frequency or magnitude from that ordinarily anticipated clinically are not AEs (e.g., onset of menstruation occurring at a physiologically appropriate time).

Clinical AEs should be described by diagnosis and not by symptoms when possible (e.g., cold, seasonal allergies, instead of “runny nose”).

An adverse reaction is any untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to the participant.

6.1.2. Serious Adverse Event (SAE) and Serious Adverse Reaction (SAR)

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

   In the case of death, the PI will request permission from the family to perform an autopsy.

b. Is life threatening

   The term life threatening in the definition of serious refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

   In general, hospitalization or emergency ward for observation and/or intervention that would not have been appropriate in the physician's office or outpatient setting signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.

   Hospitalization for elective intervention of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

   The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations

   Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive intervention in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

A SAR is defined as a SAE which is considered related to any dose of the product that is administered to the participant.

6.1.3. Suspected Unexpected Serious Adverse Reaction (SUSAR)

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is defined as an untoward and unintended response to a study drug, which is not listed in the applicable product information, and meets one of the following serious criteria: results in death, is life-threatening, requires hospitalisation or prolongation of an existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

The Reference Safety Information (RSI) of the Investigational Brochure is to serve as the basis for expectedness assessments of 'suspected' serious adverse reactions ('suspected' SARs) for expedited reporting of suspected unexpected serious adverse reactions (SUSARs). The sponsor is responsible for performing the assessment of expectedness.

6.2. Assessment of Severity (Intensity)

The classification for adverse events will follow NIH guidelines outlined in Common Terminology Criteria for Adverse Events v4.03 (CTCAE; published May 28, 2009), which includes:

6.2.1. Grade 1

A type of adverse event that is mild, usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

6.2.2. Grade 2

A type of adverse event that is moderate, usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.

6.2.3. Grade 3

A type of adverse event that is severe, interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

6.2.4. Grade 4

Life- threatening consequences; urgent intervention indicated

6.2.5. Grade 5

Results in death

6.3. Assessment of Causality

The causality assessment decisions must be made by a medically qualified doctor, as these decisions require medical and scientific judgement as well as knowledge of the participant concerned.

The Principal Investigator should then assess any relationship between an adverse event and the trial drug. Association or relatedness to the study agent will be graded as follows: 5 = unrelated, 4 = unlikely, 3 = possibly, 2 = probably, and 1 = definitely related. If an Investigator uses the WHO classification categories of causality when assessing causality, 'highly probable', 'probable', 'possible' should be regarded as related by the sponsor, while 'unlikely' and 'not' may be considered to be not related. This cause and event appraisal is to be carried out using the following classification:

- Unrelated: The adverse event is unrelated to the use of the trial drug.
- Unlikely related: There are other, more likely causes to the adverse event, and the trial drug is not suspected to play a role.
- Possibly related: A direct cause and effect between the trial drug and the adverse event is not proven, but there is a reasonable possibility that the adverse event was caused by the drug.
- Probably related: It is likely that there is a direct cause and effect relationship between the trial drug and the adverse event.
- Definitely related: When it is absolutely certain that there is a connection between the investigational gene therapy product and the Adverse Event.

A reasonable possibility of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. The Investigator will use clinical judgment to determine the relationship. Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated. The Investigator will also consult the IB in his/her assessment, as there is a specific list of anticipated Adverse Events that have been observed and reported along the clinical trial as potentially related to the study drug. For each AE or SAE, the Investigator must document in the medical notes that he/she has reviewed the AE or SAE and has provided an assessment of causality. There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to sponsor or designee. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor or designee. The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

6.4. Recording

When an AE or SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event. The Investigator will then record all relevant AE or SAE information in the participant's medical records, in accordance with the Investigator's normal clinical practice and on the appropriate form of the [e]CRF. It is not acceptable for the Investigator to send photocopies of the participant's medical records to the sponsor or designee in lieu of completion of the sponsor or designee AE or SAE [e]CRF page. There may be instances when copies of

medical records for certain cases are requested by the sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor or designee. The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

6.5. Reporting of SAEs and SARs

The sponsor, the Investigator or his designee will report all serious and unexpected adverse events to the IRB, Regulatory or Competent Authorities (i.e. CBER/FDA, OBA/NIH, AEMPS, CCAA, TGA, HREC and other) and DSMB according to regulatory requirements described as follows:

Any SAE event will be reported to the Sponsor and/or their safety representative within 24 hours. The Sponsor will then inform the DSMB within 48 hours from notification of the site to the Sponsor and before enrollment of additional participants. The DSMB will decide then on the relationship of the SAE to the study agent (as possibly, probably or definitely related to the study agent).

Any unexpected event that is fatal or life-threatening, and associated with the use of the gene transfer (SUSAR) product will be reported to Competent Authorities as soon as possible, but not later than 7 calendar days after the sponsor's initial receipt of the information. SUSARs that are unexpected and associated with the use of the gene transfer product, but are not fatal or life-threatening, will be reported to Competent Authorities as soon as possible, but not later than 15 calendar days after the sponsor's initial receipt of the information.

If, after further evaluation, a SAE initially considered not to be associated with the use of the gene transfer product is subsequently determined to be associated, then the event will be reported to the Competent Authorities within 15 days of the determination.

Relevant additional clinical and laboratory data will become available following the initial SAE report. Any follow-up information relevant to a SAE will be reported within 15 calendar days of the sponsor's receipt of the information. If a SAE occurs after the end of a clinical trial and is determined to be associated with the use of the gene transfer product, that event will be reported to the Competent Authorities within 15 calendar days of the determination.

Should a SAE deemed possibly, probably or definitely related to the study agent occur during administration, the study agent will be discontinued, appropriate treatment will be given under medical supervision and the participant will be examined as frequently as necessary thereafter until symptoms cease or stabilize.

Any SAE or study-related unanticipated problem posing risk of harm to participants or others must be reported by the Investigator to the Sponsor and/or their safety representative within 24 hours of the event detection. To report such events, a SAE reporting form must be completed by the Investigator and sent to the study sponsor or pharmacovigilance CRO as delegated. The Investigator will keep a copy of this SAE form on file at the study site. The delegated CRO will report the event to the study sponsor in a maximum period of 24 hours after SAE form reception.

Within the following 48 hours, if there is further information on the SAE or the unanticipated problem it should be provided by the Investigator as a follow-up to the initial SAE report. This may include a copy of any diagnostic information that will assist the understanding of the event. Any other significant new information on ongoing SAEs should be provided to the study sponsor or pharmacovigilance CRO delegated as soon as possible.

The final SAE report will include, but need not be limited to:

(1) The date of the event;

(2) Clinical site;

(3) The Principal Investigator;

(4) Route of administration, e.g., intramuscular;

(5) Dosing schedule;

(6) A complete description of the event;

(7) Relevant clinical observations;

(8) Relevant clinical history;

(9) Relevant tests that were or are planned to be conducted;

(10) Date of any treatment of the event; and

(11) the suspected cause of the event.

The study sponsor or pharmacovigilance CRO delegated following current law dispositions is responsible for:

- Continuously evaluating the safety of all drugs under investigation and communicating any important information regarding safety to the FDA, AEMPS and other Competent Authorities, including Ethical Committee (Comite Ético de la Investigación con medicamento - CEIm) and Authonomous Regions (Comunidades Autónomas - CCAA) involved if applicable
- Notification to the Competent Authorities in accordance with local regulations about all suspected SAEs and also unexpected SAEs regarding the drug under investigation, having occurred within the country where the clinical trial is being conducted, having occurred within this authorized clinical trial, any other clinical trial, or in a different context of use, in case these drugs are not authorized for human use.

Study sponsor is responsible to ensure that only SARs with "reasonable causal relationship" are assessed for expectedness and considered for SUSAR reporting. The following describes the general safety reporting requirements by timeline for reporting and associated type of event:

- Within 7 calendar days, any study event that is:
    - ✓ associated with the use of the study drug
    - ✓ unexpected
    - ✓ fatal or life-threatening
- Within 15 calendar days, any study event that is:
    - ✓ associated with the use of the study drug
    - ✓ unexpected and serious, but not fatal or life-threatening
    - ✓ a previous adverse event that was not initially deemed reportable but is later found to fit the criteria for reporting (reporting within 15 calendar days from when event was deemed reportable).

Should an SAE be deemed possibly, probably or definitely related to the study agent occur during administration, the study agent will be discontinued, appropriate treatment will be given under medical supervision and the participant will be examined as frequently as necessary thereafter until symptoms cease or stabilize.

A detailed Safety Management Plan (SMP) is developed for the study to define all the forms, timelines and responsibilities for SAE/SAR reporting.

6.6. Reporting of pregnancy

If a participant becomes or is found to be pregnant during the subject's participation in the study, the pregnancy will be reported to the Sponsor and/or their safety representative within 24 hours of the Investigator being aware of the pregnancy. Pregnancy in itself is not regarded as an AE and/or SAE. The pregnancy and the outcome of the pregnancy (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) will be followed and documented, even if the participant was discontinued from the study. The pregnancy and outcome will be reported using the pregnancy forms.

7. DOSING NEW PARTICIPANTS AND STOPPING/DISCONTINUATION RULES

7.1. Dose New Participants

Participants will be dosed with a 14-day interval between them, after clinical information and safety data from Day 1, 7 and 14 from the previous participant have been reviewed and communicated by the Principal Investigator to the Sponsor.

7.2. Stopping/Discontinuation Rules

Study enrollment will be halted by the investigators when two or more serious adverse events are experienced within the same or different participants that are possibly, probably, or definitely related to the study drug (SAR) (as attributed by the DSMB), or when two participants experience the same serious adverse event that is possibly, probably, or definitely related to the study drug (SAR) (as attributed by the DSMB). This will include any participant death not related to underlying disease condition, important clinical laboratory finding, or any severe local complication in the injected area related to administration of the study agent. If after review by the DSMB the decision is made to continue, the study will proceed.

Additionally, an independent Data Safety Monitoring Board (DSMB) and designated monitor will monitor safety data on a continual basis throughout the trial. The DSMB can recommend early termination of the trial for reasons of safety or further review by ethical committees and competent authorities. Further details about DSMB constitution, meeting, responsibilities and functions are described in Section 9.3.1.

In any case, if the study is halted, the Competent Authorities will be consulted prior to study restart, in the form of a substantial amendment. The protocol will be amended accordingly.

8. ETHICAL AND REGULATORY ASPECTS

This study will be conducted in accordance with the ethical principles that have their origin in the World Medical Association (WMA) Declaration of Helsinki and will be consistent with Good Clinical Practice (GCP) guidelines. It will also follow the local regulatory requirements for each country.

8.1. Ethical Review Board

Before initiating the clinical trial, this protocol and all required documents will be submitted to the relevant Institutional Review/Ethical Review Boards in each country for approval. This approval will remain in the Investigators Coordinator Archive, and a copy will be kept in the study general archive. The study will only commence after obtaining written approval from the relevant Ethical Review Boards.

Any amendment to the protocol will also be presented to the relevant Competent Authorities and Ethical Review Boards. The Ethical Review Boards, and Competent Authorities (where required), will also be notified in case of any SAEs, according to law dispositions.

8.2. Informed Consent

There is a wide spectrum of severity of this disorder. Based on the known natural history of this currently untreatable, progressive and neurodegenerative disease, patients of any age with the severe phenotype of Sanfilippo A disease will not have the cognitive and executive capacity to enable them to give their informed consent for participation in the clinical trial. The sponsor of this proposed clinical trial intends to include only an informed consent form (ICF) that will be suitable for caregivers /parents of adults and children with Sanfilippo A disease. There is no need for an assent form and informed consent for children and adults with this condition as they are unlikely to be able to understand the patient information sheet and provide informed consent or assent.

As a consequence, all parents and/or legal guardians of the participant will be provided with an Information Sheet and/or Consent Form describing this study and providing sufficient information for participants to make an informed decision about the participation of their represented participant in this study. Where required, consent will be sought from the parents and/or legal guardian of the participant. The Informed Consent Forms (ICFs) and Patient Informed Consent Forms (PICFs) will include all elements required by ICH, GCP and applicable regulatory requirements.

The Information Sheet and/or Consent Form will be submitted with the protocol for review and approval by the relevant Ethical Review Board for the study in each country. The formal consent of a participant, using the Informed Consent Form approved by the relevant Ethical Review Board, must be obtained before that participant undergoes any study procedure. The consent form must be signed by the participant's parent/legal guardian, and the Investigator-designated research professional obtaining the consent. Where required by the relevant Ethical Review Board, a witness may sign the consent form.

If there is a need to re-consent participants, the Investigator or a person designated by the Investigator should inform the participant's parents/legal guardian of any new information

relevant to their willingness to continue to provide consent for their participation in the study, before obtaining the written consent.

8.3. Confidentiality Information

Participants will be assigned a unique identifier by the sponsor. The participant code will be a composite of two numbers:

- The first number with three digits will correspond to the site number such as 001, 002, 003.
- The second number with two digits will correspond to the participant number for each site that will be assigned sequentially (01, 02, 03, 04, 05, 10) to all participants enrolled.

Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The collection and processing of personal data from the participants enrolled in this study will be limited to those data that are necessary to achieve the study objectives previous described. The date of birth and age of the participant at screening will be collected to ensure that the appropriate age-based assessments are performed throughout the study. The data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Explicit consent for the processing of personal data will be obtained from the participating participant before data collection, if applicable, and this consent should also address the transfer of the data to other entities and countries.

The trial monitor, the Sponsor, the Sponsor(s)'s auditor, the relevant Ethical Review Board, and the Competent Authorities should have direct access to all requested study-related records and agree to keep the identity of study participants confidential. The sponsor shall comply with all local regulatory requirements in the United States, Spain and Australia.

Information about study participants will be kept confidential and managed according to the applicable laws in each country.

8.4. Compensation for Participants

Participants will receive reimbursement for the travel expenses for attending the visits, if necessary. Travel expenses include but are not restricted to transportation (and associated costs), accommodations, and meals for the participant and their parents/legal guardian and siblings (if necessary). To receive this refund, the participant's parents/legal guardian must follow the process for reimbursement provided by the Investigators at the beginning of the study.

8.5. Insurance Policy

The Sponsor will provide insurance and/or indemnity in accordance with the applicable regulatory requirements for each of the participating sites.

8.6. Notifications to Health Authorities

The amendments to the protocol will be made only when such changes have been agreed in writing, and signed, by the principal Investigators and the sponsor. The protocol changes may represent changes in the informed consent of all participants, both prospective and already included. The participant and/or parent/legal guardian must sign a new consent if such changes occur. Any subsequent protocol amendments will be submitted to the relevant Ethical Review Boards and Competent Authorities in accordance with the local regulatory requirements in each country. When an amendment to a protocol substantially alters the study design or increases potential risk to the study participant, the Informed Consent Form will be revised and the participant's consent to continue participation will again be obtained.

Deviations from the Protocol should be avoided, however if a deviation from the protocol is required for the safety of a participant the deviation will be made only for that participant. Within 48 hours of the deviation the principal Investigator and/or treating Investigator must inform the study sponsor or delegated CRO regarding the protocol deviation and rationale for the deviation. The principal Investigator and the sponsor will determine if the participant who has deviated from the protocol is able to continue in the study. These deviations will be described in the participant medical record and in the case report form, specifying the circumstances leading to the deviation. Where required by local regulations, the Institutional Review/Ethical Review Board and/or the Competent Authorities in the country where the deviation occurred will be informed.

9. STUDY REPORTS

9.1. Final Study Report

The sponsor will prepare a final Clinical Study Report that will include all data, results and observations through the final study visit for the final participant but will not include long-term follow-up information. The summary of this report will be submitted to the relevant authorities.

The management, or publication, of any information relevant to this clinical trial will be in accordance with local and international regulatory requirements.

9.2. Annual Study Reports

According to national legislation, the Study sponsor or delegated CRO will submit information set forth as follows:

a. Clinical Trial Annual Report. This will be a brief summary of the status of the trial in progress or completed during the previous year. The summary will include information required by application relations of each country where the trial is being conducted.
b. Annual Safety Report or Development safety update report (DSUR). An annual summary of all serious adverse events for an active compound in clinical evaluation with a safety evaluation relating to the ongoing study(ies). US and EU regulators consider that the DSUR, submitted annually, would meet national and regional requirements of each country where the trial is being conducted.

   For advanced therapy products such as gene therapy products, the long-term follow-up section should provide information from long-term follow-up of participants from clinical trials of investigational drugs. When the development program is completed and long-term follow-up is the only ongoing activity generating data for the DSUR, this could be the only section where new information is presented.

c. Update Investigator's brochure (IB). At least once per year according to Good Clinical Practice. This update should include any relevant new (including safety related) data on IMP, toxicology, clinical experience, etc.

9.3. Data Safety Monitoring Plan

9.3.1. The Data Safety Monitoring Board

A DSMB will be established and act in an advisory capacity to review participant safety and study progress throughout the duration of the study. The DSMB will accomplish this advisory capacity through preplanned and possibly ad hoc reviews of accumulated data. Based on the findings of these reviews, the DSMB will make recommendations to the Sponsor regarding the study(ies). The Sponsor will be responsible for discussing and implementing the DSMB recommendations, if considered appropriate.

Primary Responsibilities of the DSMB are to protect the safety and privacy of study participants, evaluate the progress of the study, monitor all SAEs and assess the risk/benefit balance in relation to the Investigational Medicinal Product.

The full scope of the DSMB members' and relevant parties' responsibilities, the organizational and communication structure, frequency and conduct of the meetings, and its membership will be documented in a DSMB charter. Study specific requirements will be documented and attached to the charter.

9.3.2. DSMB Reporting and Meetings

The DSMB will hold planned meetings during the course of the study. DSMB reviews will occur at least once per a year (or at other interval determined by the DSMB and based on study activities). The time period will encompass the start of the study with the first participant dosed and end with the conclusion of all study activities.

The Sponsor (or designee) will provide the DSMB members with a report describing the status of the study and the current safety information prior to each DSMB meeting. The details of the data being included in the report to the DSMB will be documented in the charter.

9.3.3. Membership

DSMB will be comprised of a minimum of 4 members. DSMB members shall be completely independent of the Investigators and have no financial, scientific, or other conflicts of interest with the clinical studies. The DSMB is integrated by recognized experts and representatives from different fields relevant for the study.

9.4. Clinical Monitoring of the Study

The study will be monitored in compliance with the relevant regulation of each country, (for example parts of 21 CFR and ICH GCP Guidelines). The procedures outlined in the protocol and case report forms will be carefully reviewed by the PI and staff prior to study initiation to ensure appropriate interpretation and implementation. No deviations from the protocol shall

be made except in emergency situations where alternative treatment is necessary for the protection, proper care and wellbeing of participants.

Amendments will be submitted to the site's local IRB/EC for their review and approval prior to implementation. When an amendment to a protocol substantially alters the study design or increases potential risk to the study participant, the Informed Consent Form will be revised and if applicable, participant's consent to continue participation will again be obtained.

9.4.1. Data Management and Study Forms

All data and observations will be documented on Case Report Forms (CRF) by source documentation. A Monitor will have access to the data to monitor adherence to the protocol and to applicable regulations, and the maintenance of adequate and accurate clinical records. A CRF will be completed for every participant that was registered for participation in the study.

Case Report Forms will be reviewed in detail by the Monitor on a regular basis for which the Monitor will have access to participant medical records, laboratory data, and other source documentation. Monitor will make a decision as to data acceptability. If errors or omissions are found in the course of a data audit, or if clarification of data is required, the Case Report Form(s) in question will be corrected by the PI or his designee. Data Resolution may be generated on

omissions or clarifications, to be completed, signed and dated, and maintained as a part of the CRF.

The PI will sign and accept the indicated Case Report Form. This signature will indicate that thorough inspection of the data therein has been made and will thereby certify the contents of the form.

The Sponsor will design a data collection system for managing the clinical trial. A web-based database will be created and managed by authorized users. CRFs will be transcribed to this web-based database. Data will be extracted from source documents (lab reports, echo reports, etc.) and transferred to the database as well. All source documents will be kept in a Participant Research Chart.

An external Contract Research Organization (CRO) may also monitor the study on a regular basis to make sure the study is conducted in compliance with all regulatory aspects of the protocol.

10. SAMPLE MANAGEMENT

In Spain, biological samples are regulated according to the Law 14/2007 of Biomedical Research which treatment regimen is developed by Royal Decree 1716/2011, of November 18, by which the basic requirements for authorization and operation of biobanks are established for biomedical research and treatment of biological samples of human origin, and the operation and organization of the National Registry of Biobanks for biomedical research are regulated. In addition, because the samples will be sent to be analyzed and stored to the USA, it needs to be in compliance with Royal Decree 65/2006, of 30 January, laying down requirements for the import and export of biological samples.

Sample management will be performed according to National Statement on Ethical Conduct in Human Research 2007- Update (https://www.nhmrc.gov.au/guidelines-publications/e72)

Any future research not related to the objectives of this clinical trial, in which the use of these biological samples is proposed must be approved by the IRB/EC. Future research may have different purposes, although the biological samples used in this study are to be kept only as long as they are necessary for the purposes for which they were collected.

11. GMO RISK MANAGEMENT

For Europe, in regard to risk-based management plan for this type of advanced therapy medicinal products (EMA/CAT/CPWP/686637/2011), environmental risk assessment is described at the end of this point and other potential risk factors due to natural characteristics of the virus from which the vector is derived are described in the following paragraphs.

The genetically modified organism (GMO), scAAV9.U1A.SGSH, is a recombinant vector derived from adeno-associated virus serotype 9 (AAV9), The vector is replication defective due to complete replacement of adeno-associated viral genes with a cassette of expression for human SGSH. The complete description of vector elements and vector production is described in the Investigational Brochure; however, some elementary risk factors are described here.

This vector is classified as nonintegrating and nonpathogenic by research publication and regulatory guidelines (EMA/CAT/190186/2012), so insertional mutagenesis is not a risk concern with the recombinant vector. The potential risk for insertional oncogenesis is negligible. Therefore, there is minimal risk for potential chromosomal integration and resulting genotoxicity.

It is worth mentioning that there is minimal risk of the vector for latency/reactivation and/or mobilization or potential for recombination/re-assortment. Vector tropism and immunogenicity are equivalent to wild type AAV9 virus. The genetic modification does not allow the viral vector to revert to wild type virus due to the absence of viral genes and inability to replicate or spread further from the transduced cell. Genetic stability is ensured due to similar size of the wild-type and recombinant viral expression cassettes, so genome rearrangements are not expected. The vector genome is completely sequenced in the DNA plasmid used for its generation.

Recombinant AAV vectors are nonpathogenic, lack toxicity and avirulent and they do not activate latent virus and are not able to colonize other organisms. The most commonly known host range includes humans and nonhuman primates.

Wild type AAV is not classified in Risk Groups 2, 3 or 4 in the European Union (EU) according to Directive 2000/54/EC on the protection of workers from risks related to exposure to biological agents at work. Therefore, it is most appropriately designated as a Risk Group 1 biological agent, defined in the EU as ‘one that is unlikely to cause human disease’. Additionally, AAVs are not assigned an Advisory Committee on Dangerous Pathogens (ACDP) category, so recombinant AAV viruses are also classified biosafety Group/Class 1. Similar classifications of hazard have been assigned to AAV according to the definitions of the World Health Organisation (WHO), and in the USA, Canada and Australia. This all means that the risk is null or insignificant.

However, the hospital staff will receive, store, manipulate and destroy the gene therapy product and all biological samples (potentially containing also GMO) under biosafety rules type 1 (BSL1). Hospital will follow internal procedures for biological product management. Briefly, the recombinant adeno-associated vector will be received by the pharmacy department according to the instructions of the sponsor in the Pharmacy Manual. The storage will be performed in a -80ºC freezer located at pharmacy with a limited access. The final product preparation (defrost, potential dilution and syringe preparation) will be performed in a biosafety cabinet type 2 (vertical flow for complete protection of environment and hospital staff) if required by the Competent Authorities. The syringe prepared for administration will be transported to the individual room where the participant is hospitalized in a proper box to avoid spills and labeled

as "containing GMO". All material used for GMO delivery and manipulation (empty vials, guide tube, cannula, stylet, injection needle and syringe) will be destroyed following internal procedures for biological management and BSL1. In addition, any disposable surgical instruments or other materials used during the administration procedure or collection of body fluids will be disposed according to standard biosafety practice of the institution. All non-disposable surgical equipment will be cleaned using a chemical disinfectant with proven viricidal activity (e.g. hypochlorite 1% solution) and then sterilized by autoclaving according to standard practice of the institution.

All health personnel involved in this trial will use biosafety practices level 1 during transport prior to and after administration and final disposal. In case of spillover, the perimeter of the spill will be limited with paper towels and appropriate virucidal agent will be used to clean the area: As all vectors based on adeno-associated viruses, scAAV9.U1A.SGSH is susceptible to appropriate virucidal disinfectants with activity for non-enveloped viruses such as 1-10% sodium hypochlorite (for at least 20 minutes), alkaline solutions at pH >9, 5% phenol, heat (>80°C for 60 minutes), UV radiation and extreme pHs (<2 and >12). Effective disinfectants require a minimum of 20 minutes contact time. In case of injury, the injured site will be disinfected appropriately according to the best biosafety practice standard and internal procedures.

Participants will be admitted to the Hospital one by one, for a single intravenous administration. Participants will stay in an individual hospital room for at least 48 hours after gene transfer for close monitoring and then they will come back to the hospital for periodic visits (Days 7, 14, 30, etc). Testing for the release of vector will be conducted until the participant shows two consecutive negative results in previously collected samples.

According to legislation for environmental risk assessments (guidelines EMEA/CHMP/ICH/449035/2009 and EMEA/CHMP/GTWP/125491/2006), shedding is defined as the dissemination of the virus/vector through secreta and/or excreta of the participant. Assessment of the shedding can be utilized to understand the potential risk associated with transmission to third parties and potential risk to the environment. It is worth mentioning that a limited release of the GMO to wastewater is expected after the administration to the participants. Preclinical data in relevant animal model for vector transduction (mice) is showing a positive shedding in feces and urine samples for a period of 35 days with a very low number of vector genomes. Additionally, the pH and biological conditions in urine and feces diminish the potential survival of the genetically modified organism. However, the wastewater is not an ecosystem where GMO can survive for a long period of time. It is expected that GMO will be degraded after administration to humans by endogenous protein and DNA catabolic pathways. Shed vector DNA is expected not to be stable in wastewater. Taking into account these characteristics and the GMO replication incapacity, no interaction of the GMO with the flora, fauna, livestock or migratory species is expected.

The potential GMO release to the environment will be analyzed in serum and biological fluids samples obtained from all treated participants according to the protocol of the clinical trial. As suggested by regulatory guidelines, samples will be taken more frequently in the first days following administration in order to detect a transient shedding profile. Serum, saliva, urine and feces will be collected at Day 0, 1, 2, 7, 14, and 30 after vector administration. Vector shedding analysis will continue to be collected and analyzed until two consecutive negative samples are collected or completion of the study by the participant, whichever comes first. Analysis will be

performed in order to obtain multiple consecutive negative measurements as suggested. Guidelines established that quantitative assays are preferred for shedding studies as this will aid in quantifying the probability of transmission. In fact, the use of quantitative PCR assays to detect viral/vector genetic material is recommended, because they are sensitive, reproducible and rapid. The samples will be analyzed for GMO detection and quantification based on a specific qPCR. It is worth mentioning that ELISpot, ELISA and PBLs samples will also be obtained to monitor the humoral and T cellular response that will also be assayed to monitor the indirect effect of the GMO presence by means of antibodies and T reactive cells.

The risk of horizontal gene transfer to bacteria is most likely minimal but cannot be excluded. Even if horizontal gene transfer occurred, the sequences would not confer a selective advantage to other organisms (such as bacteria) since scAAV9.U1A.SGSH does not contain any prokaryotic promoters, any antibiotic- or other types of resistance genes or any genes, which would enhance or constrain their growth. Therefore, it is unlikely that scAAV9.U1A.SGSH would interfere with the control of pathogenic microorganisms or that it would have an effect on the natural dynamics of microbial populations or the biogeochemical cycles at any given site in the environment.

The GMO is not pathogenic, and no side-effects have been reported for the environment or human health after the release of similar GMOs (adeno-associated virus from serotypes 2, 5, 8 and 9), thus no undesirable effects are expected. However, if an undesirable effect occurs then the use of scAAV9.U1A.SGSH would-be put-on hold until the effects are fully assessed, and measures are put in place to mitigate further risks. In Spain, authorization, notification and report to the Ministry of Agriculture, Food and Environment (CIOMG) is part of the study management which fulfills with the applicable voluntary release defined in Law 9/2003, of April 25, approving the legal regime of the confined use, voluntary release and marketing of genetically modified organisms.

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STATEMENT OF COMPLIANCE

Protocol Title: 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

Protocol Number: ABT-003 Version 5.0 22 September 2022

INVESTIGATOR SIGNATURE:

I have read the protocol and agree to conduct the study as detailed in this protocol and in compliance with the Declaration of Helsinki, Good Clinical Practice (GCP), and all applicable regulatory requirements and guidelines.

_____

Investigator Signature Date

Printed Name: _____

SPONSOR SIGNATURE:

As the Sponsor representative, I confirm that Ultragenyx Pharmaceutical Inc. will comply with all Sponsor obligations as detailed in this protocol and in compliance with the Declaration of Helsinki, GCP, and all applicable regulation requirements and guidelines. I will ensure that the Investigator is informed of all relevant information that becomes available during the conduct of this study.

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PPD Date

Executive Director, Global Clinical Development
Ultragenyx Pharmaceutical Inc.