

**Clinical trial results:****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****Summary**

EudraCT number	2018-000504-42
Trial protocol	ES
Global end of trial date	10 March 2022

Results information

Result version number	v3
This version publication date	25 June 2023
First version publication date	04 October 2022
Version creation reason	• New data added to full data set Final data added
Summary attachment (see zip file)	Results Extension Notification (Notification of Extension of CSR Submission and Posting of Study Results.pdf)

Trial information**Trial identification**

Sponsor protocol code	ABT-003
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04088734
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ultragenyx Pharmaceutical Inc.
Sponsor organisation address	60 Leveroni Court, Novato, United States, California 94949
Public contact	Ultragenyx Pharmaceutical, Inc., Patient Advocacy, +1 415 756-8657, Trialrecruitment@ultragenyx.com
Scientific contact	Medical Information, Ultragenyx Pharmaceutical, Inc., +1 888 756-8657, medinfo@ultragenyx.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-002206-PIP02-19
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	10 March 2022
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	10 March 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and efficacy of ABO-102 (also known as UX111) in patients with middle and advanced phases of mucopolysaccharidosis (MPS) IIIA disease.

Protection of trial subjects:

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, Good Clinical Practice (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.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 September 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	United States: 1
Country: Number of subjects enrolled	Australia: 1
Worldwide total number of subjects	5
EEA total number of subjects	3

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	5
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The screening evaluations will take place over two visits (preferentially two weeks apart). 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.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	scAAV9.U1a.hSGSH, 3x10 ¹³ vg/kg
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Arm description:

An intravenous injection of ABO-102 (scAAV9.U1a.hSGSH) via peripheral limb vein at a dose of 3.0 x 10¹³ vg/kg

Arm type	Experimental
Investigational medicinal product name	ABO-102
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

3 x 10¹³ vg/kg of ABO-102 delivered one time through a venous catheter inserted into a peripheral limb vein.

Number of subjects in period 1	scAAV9.U1a.hSGSH, 3x10 ¹³ vg/kg
Started	5
Completed	0
Not completed	5
Other, not specified	5

Baseline characteristics

Reporting groups

Reporting group title	scAAV9.U1a.hSGSH, 3x10 ¹³ vg/kg
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Reporting group description:

An intravenous injection of ABO-102 (scAAV9.U1a.hSGSH) via peripheral limb vein at a dose of 3.0 x 10¹³ vg/kg

Reporting group values	scAAV9.U1a.hSGSH, 3x10 ¹³ vg/kg	Total	
Number of subjects	5	5	
Age categorical Units: Subjects			
Age continuous Units: months arithmetic mean standard deviation	68.4 ± 34.49	-	
Gender categorical Units: Subjects			
Female	1	1	
Male	4	4	
Race Units: Subjects			
White	5	5	
Ethnicity Units: Subjects			
Hispanic or Latino	1	1	
Not Hispanic or Latino	4	4	

End points

End points reporting groups

Reporting group title	scAAV9.U1a.hSGSH, 3x10 ¹³ vg/kg
Reporting group description:	
An intravenous injection of ABO-102 (scAAV9.U1a.hSGSH) via peripheral limb vein at a dose of 3.0 x 10 ¹³ vg/kg	

Primary: Incidence, Type and Severity of Related Treatment-Emergent Adverse Events (TEAEs) by Time Frame

End point title	Incidence, Type and Severity of Related Treatment-Emergent Adverse Events (TEAEs) by Time Frame ^[1]
End point description:	
An adverse event (AE) is any untoward medical occurrence or unintended change from the time informed consent form (ICF) is signed, including inter-current illness that occurs during the course of a clinical trial after treatment has started, whether considered related to treatment or not. TEAEs are those that occurred after the start of study drug. Related adverse events were categorized as possible, probable, or definitely.	
End point type	Primary
End point timeframe:	
From the first dose of study drug to <30 days postdose, Day 30, 60, 90, 180 and Month 12	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive statistics are presented per protocol.

End point values	scAAV9.U1a.hSGSH, 3x10 ¹³ vg/kg			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: subjects				
< 30 days; Possible; Mild	1			
< 30 days; Possible; Moderate	0			
< 30 days; Possible; Severe	0			
< 30 days; Probable; Mild	2			
< 30 days; Probable; Moderate	0			
< 30 days; Probable; Severe	1			
< 30 days; Definitely; Mild	1			
< 30 days; Definitely; Moderate	0			
< 30 days; Definitely; Severe	0			
30 - < 60 days; Possible; Mild	0			
30 - < 60 days; Possible; Moderate	0			
30 - < 60 days; Possible; Severe	0			
30 - < 60 days; Probable; Mild	2			
30 - < 60 days; Probable; Moderate	0			
30 - < 60 days; Probable; Severe	1			
30 - < 60 days; Definitely; Mild	1			
30 - < 60 days; Definitely; Moderate	0			
30 - < 60 days; Definitely; Severe	0			
60 - < 90 days; Possible; Mild	0			

60 - < 90 days; Possible; Moderate	0			
60 - < 90 days; Possible; Severe	0			
60 - < 90 days; Probable; Mild	1			
60 - < 90 days; Probable; Moderate	0			
60 - < 90 days; Probable; Severe	0			
60 - < 90 days; Definitely; Mild	0			
60 - < 90 days; Definitely; Moderate	0			
60 - < 90 days; Definitely; Severe	0			
90 - < 180 days; Possible; Mild	0			
90 - < 180 days; Possible; Moderate	0			
90 - < 180 days; Possible; Severe	0			
90 - < 180 days; Probable; Mild	0			
90 - < 180 days; Probable; Moderate	1			
90 - < 180 days; Probable; Severe	0			
90 - < 180 days; Definitely; Mild	0			
90 - < 180 days; Definitely; Moderate	0			
90 - < 180 days; Definitely; Severe	0			
180 - < 12 months; Possible; Mild	0			
180 - < 12 months; Possible; Moderate	0			
180 - < 12 months; Possible; Severe	1			
180 - < 12 months; Probable; Mild	0			
180 - < 12 months; Probable; Moderate	0			
180 - < 12 months; Probable; Severe	0			
180 - < 12 months; Definitely; Mild	0			
180 - < 12 months; Definitely; Moderate	0			
180 - < 12 months; Definitely; Severe	0			

Statistical analyses

No statistical analyses for this end point

Primary: Incidence, Type and Severity of Serious Adverse Events (SAEs) by Time Frame

End point title	Incidence, Type and Severity of Serious Adverse Events (SAEs) by Time Frame ^[2]
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End point description:

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

- Results in death
- Is life threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent disability/incapacity
- Is a congenital anomaly/birth defect
- 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.

Relationship to study drug was defined as unrelated, unlikely, possible, probable, or definitely.

End point type	Primary
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End point timeframe:

From signing of informed consent through Day 60, 90, 180 and up to Day 454 (> 12 months)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive statistics are presented per protocol.

End point values	scAAV9.U1a.hS GSH, 3x1013 vg/kg			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: subjects				
60 - < 90 days; Unrelated; Mild	0			
60 - < 90 days; Unrelated; Moderate	0			
60 - < 90 days; Unrelated; Severe	0			
60 - < 90 days; Unlikely; Mild	0			
60 - < 90 days; Unlikely; Moderate	0			
60 - < 90 days; Unlikely; Severe	1			
60 - < 90 days; Possible; Mild	0			
60 - < 90 days; Possible; Moderate	0			
60 - < 90 days; Possible; Severe	0			
60 - < 90 days; Probable; Mild	0			
60 - < 90 days; Probable; Moderate	0			
60 - < 90 days; Probable; Severe	0			
60 - < 90 days; Definite; Mild	0			
60 - < 90 days; Definite; Moderate	0			
60 - < 90 days; Definite; Severe	0			
90 - < 180 days; Unrelated; Mild	0			
90 - < 180 days; Unrelated; Moderate	0			
90 - < 180 days; Unrelated; Severe	1			
90 - < 180 days; Unlikely; Mild	0			
90 - < 180 days; Unlikely; Moderate	0			
90 - < 180 days; Unlikely; Severe	1			
90 - < 180 days; Possible; Mild	0			
90 - < 180 days; Possible; Moderate	0			
90 - < 180 days; Possible; Severe	0			
90 - < 180 days; Probable; Mild	0			
90 - < 180 days; Probable; Moderate	0			
90 - < 180 days; Probable; Severe	0			
90 - < 180 days; Definite; Mild	0			
90 - < 180 days; Definite; Moderate	0			
90 - < 180 days; Definite; Severe	0			
180 days - < 12 months; Unrelated; Mild	0			
180 days - < 12 months; Unrelated; Moderate	0			
180 days - < 12 months; Unrelated; Severe	0			
180 days - < 12 months; Unlikely; Mild	0			
180 days - < 12 months; Unlikely; Moderate	0			
180 days - < 12 months; Unlikely; Severe	0			
180 days - < 12 months; Possible; Mild	0			
180 days - < 12 months; Possible; Moderate	0			

180 days - < 12 months; Possible; Severe	1			
180 days - < 12 months; Probable; Mild	0			
180 days - < 12 months; Probable; Moderate	0			
180 days - < 12 months; Probable; Severe	0			
180 days - < 12 months; Definite; Mild	0			
180 days - < 12 months; Definite; Moderate	0			
180 days - < 12 months; Definite; Severe	0			
>= 12 months; Unrelated; Mild	0			
>= 12 months; Unrelated; Moderate	0			
>= 12 months; Unrelated; Severe	1			
>= 12 months; Unlikely; Mild	0			
>= 12 months; Unlikely; Moderate	0			
>= 12 months; Unlikely; Severe	0			
>= 12 months; Possible; Mild	0			
>= 12 months; Possible; Moderate	0			
>= 12 months; Possible; Severe	0			
>= 12 months; Probable; Mild	0			
>= 12 months; Probable; Moderate	0			
>= 12 months; Probable; Severe	0			
>= 12 months; Definite; Mild	0			
>= 12 months; Definite; Moderate	0			
>= 12 months; Definite; Severe	0			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline (BL) in Multiples of Normal of Liver and Spleen Volumes After Treatment

End point title	Change From Baseline (BL) in Multiples of Normal of Liver and Spleen Volumes After Treatment ^[3]
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End point description:

As Measured by Magnetic Resonance Imaging (MRI).

Body Surface Area (BSA) (m²)=(Height(cm) * Weight (kg))/3600)^{1/2}.

Normal Liver Volume=(689.9 * BSA (m)) - 24.7.

Normal Spleen Volume (mL)=(4.6 * Weight (kg)) + 0.7.

Liver Volume (multiples of normal)=Subject Liver Volume (mL)/Normal Liver Volume (mL).

Spleen Volume (multiples of normal)=Subject Spleen Volume (mL)/Normal Spleen Volume (mL).

[1] Baseline value of multiple of normal is calculated using the baseline values of the Liver volume/Spleen Volume/Height and Weight.

End point type	Primary
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End point timeframe:

Baseline, Day 30, 180, Month 12

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive statistics are presented per protocol.

End point values	scAAV9.U1a.hS GSH, 3x1013 vg/kg			
Subject group type	Reporting group			
Number of subjects analysed	5 ^[4]			
Units: multiples of normal				
arithmetic mean (standard deviation)				
Liver volume: change from BL to Day 30; n=3	-0.4200 (± 0.08876)			
Liver volume: change from BL to Day 180; n=3	-0.4543 (± 0.31560)			
Liver volume: change from BL to Month 12; n=2	-0.1765 (± 0.17466)			
Spleen volume: change from BL to Day 30; n=4	-0.0603 (± 0.19257)			
Spleen volume: change from BL to Day 180; n=3	-0.2253 (± 0.53267)			
Spleen volume: change from BL to Month 12; n=2	-0.1330 (± 0.18102)			

Notes:

[4] - n=participants with an assessment at baseline and given time point

Statistical analyses

No statistical analyses for this end point

Primary: Change From BL in Cerebrospinal Fluid (CSF) Heparan Sulfate Levels After Treatment

End point title	Change From BL in Cerebrospinal Fluid (CSF) Heparan Sulfate Levels After Treatment ^[5]
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End point description:

End point type	Primary
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End point timeframe:

Baseline, Day 30, 180, Month 12

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive statistics are presented per protocol.

End point values	scAAV9.U1a.hS GSH, 3x1013 vg/kg			
Subject group type	Reporting group			
Number of subjects analysed	5 ^[6]			
Units: nmol/mL				
arithmetic mean (standard deviation)				
Change from BL to Day 30; n=5	-0.120 (± 0.0837)			
Change from BL to Day 180; n=3	-0.183 (± 0.0289)			
Change from BL to Month 12; n=1	-0.100 (± 99999)			

Notes:

[6] - n=number of participants with an assessment; 99999=not applicable (1 participant analyzed)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Plasma Heparan Sulfate After Treatment

End point title	Change From Baseline in Plasma Heparan Sulfate After Treatment
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End point description:

End point type	Secondary
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End point timeframe:

Baseline, Day 30, Day 180, Month 12

End point values	scAAV9.U1a.hS GSH, 3x1013 vg/kg			
Subject group type	Reporting group			
Number of subjects analysed	5 ^[7]			
Units: pmol/mL				
arithmetic mean (standard deviation)				
Change from Baseline to Day 30; n=5	-17.5 (± 17.68)			
Change from Baseline to Day 180; n=4	-31.0 (± 9.62)			
Change from Baseline to Month 12; n=2	-25.0 (± 7.07)			

Notes:

[7] - n=number of participants at given time point

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Urine Glycosaminoglycans After Treatment

End point title	Change From Baseline in Urine Glycosaminoglycans After Treatment
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End point description:

End point type	Secondary
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End point timeframe:

Baseline, Day 30, Day 180, Month 12

End point values	scAAV9.U1a.hS GSH, 3x1013 vg/kg			
Subject group type	Reporting group			
Number of subjects analysed	5 ^[8]			
Units: mg/mmol creatinine				
arithmetic mean (standard deviation)				
Change from Baseline to Day 30; n=4	-14.5 (± 9.33)			

Change from Baseline to Day 180; n=3	-13.7 (± 9.81)			
Change from Baseline to Month 12; n=1	-4.0 (± 99999)			

Notes:

[8] - n=participants with an assessment at given time point; 99999=not applicable (1 participant analyzed)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Urine Heparan Sulfate After Treatment

End point title	Change From Baseline in Urine Heparan Sulfate After Treatment
End point description:	
End point type	Secondary
End point timeframe:	
Baseline, Day 30, Day 180, Month 12	

End point values	scAAV9.U1a.hS GSH, 3x1013 vg/kg			
Subject group type	Reporting group			
Number of subjects analysed	5 ^[9]			
Units: µmol/mmol creatinine				
arithmetic mean (standard deviation)				
Change from Baseline to Day 30; n=4	-0.95 (± 0.676)			
Change from Baseline to Day 180; n=3	-0.63 (± 0.651)			
Change from Baseline to Month 12; n=1	0.60 (± 99999)			

Notes:

[9] - n=participants with an assessment at given time point; 99999=not applicable (1 participant analyzed)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Cerebrospinal Fluid (CSF) N-Sulfoglucosamine Sulfohydrolase (SGSH) Enzyme Activity Levels After Treatment

End point title	Change From Baseline in Cerebrospinal Fluid (CSF) N-Sulfoglucosamine Sulfohydrolase (SGSH) Enzyme Activity Levels After Treatment
End point description:	
End point type	Secondary
End point timeframe:	
Baseline, Day 30, Day 180, and Month 12	

End point values	scAAV9.U1a.hS GSH, 3x1013 vg/kg			
Subject group type	Reporting group			
Number of subjects analysed	5 ^[10]			
Units: nmol/17 h/mL				
arithmetic mean (standard deviation)				
Change from Baseline to Day 30; n=5	2.662 (± 5.9524)			
Change from Baseline to Day 180; n=3	-3.297 (± 5.7100)			
Change from Baseline to Month 12; n=1	0.000 (± 99999)			

Notes:

[10] - n=participants with an assessment at given time point; 99999=not applicable (1 participant analyzed)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Heparan N-sulfatase (type A) After Treatment

End point title	Change from Baseline in Heparan N-sulfatase (type A) After Treatment
End point description:	
End point type	Secondary
End point timeframe:	
Baseline, Day 30, Day 180, Month 12	

End point values	scAAV9.U1a.hS GSH, 3x1013 vg/kg			
Subject group type	Reporting group			
Number of subjects analysed	5 ^[11]			
Units: nmol/24hr/mg				
arithmetic mean (standard deviation)				
Change from Baseline to Day 30; n=5	0.578 (± 1.1299)			
Change from Baseline to Day 180; n=3	0.000 (± 0.0000)			
Change from Baseline to Month 12; n=2	0.025 (± 0.0354)			

Notes:

[11] - n=participants with an assessment at given time point

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Plasma SGSH After Treatment

End point title Change from Baseline in Plasma SGSH After Treatment

End point description:

End point type Secondary

End point timeframe:

Baseline, Day 30, Day 180, Month 12

End point values	scAAV9.U1a.hS GSH, 3x1013 vg/kg			
Subject group type	Reporting group			
Number of subjects analysed	5 ^[12]			
Units: nmol/17 h/mL				
arithmetic mean (standard deviation)				
Change from Baseline to Day 30; n=5	6.50 (± 8.682)			
Change from Baseline to Day 180; n=4	0.88 (± 1.825)			
Change from Baseline to Month 12; n=2	0.05 (± 0.495)			

Notes:

[12] - n=participants with an assessment at given time point

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Brain Volumes After Treatment

End point title Change From Baseline in Brain Volumes After Treatment

End point description:

As measured by MRI

End point type Secondary

End point timeframe:

Baseline, Month 12

End point values	scAAV9.U1a.hS GSH, 3x1013 vg/kg			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: mL				
arithmetic mean (standard deviation)				
Change in amygdala volume	-0.635 (± 0.2333)			
Change in corpus callosum volume	0.285 (± 0.5445)			

Change in CSF volume	1.290 ($\pm$ 0.5091)			
Change in total cerebellar gray matter volume	-7.210 ($\pm$ 7.2125)			
Change in total cerebellar white matter volume	0.985 ($\pm$ 4.0234)			
Change in total brain volume	-157.705 ($\pm$ 44.6114)			
Change in total cerebral volume	-152.365 ($\pm$ 59.1353)			
Change in total cerebral gray matter volume	-145.975 ($\pm$ 81.0981)			
Change in total cortical volume	-144.170 ($\pm$ 84.9235)			
Change in total cerebellar volume	-6.225 ($\pm$ 11.2218)			
Change in total cerebral white matter volume	-6.385 ($\pm$ 21.9698)			
Change in total gray matter volume	-153.190 ($\pm$ 73.8927)			
Change in total intercranial volume	-122.245 ($\pm$ 40.0576)			
Change in total white matter volume	-5.400 ($\pm$ 25.9932)			
Change in ventricular volumes	34.165 ($\pm$ 5.0417)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Brain Volumes After Treatment: Average Total Cortical Thickness

End point title	Change From Baseline in Brain Volumes After Treatment: Average Total Cortical Thickness
End point description:	
As measured by MRI	
End point type	Secondary
End point timeframe:	
Baseline, 12 months	

End point values	scAAV9.U1a.hS GSH, 3x1013 vg/kg			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: mm				
arithmetic mean (standard deviation)	-0.455 ($\pm$ 0.2475)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Sleep Pattern as Measured by the Modified Children's Sleep Habits Questionnaire (CSHQ) Subscore Total at Day 180 and Month 12

End point title	Change From Baseline in Sleep Pattern as Measured by the Modified Children's Sleep Habits Questionnaire (CSHQ) Subscore Total at Day 180 and Month 12
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End point description:

CSHQ is a caregiver-completed, 35-item questionnaire that assesses the frequency of behaviors associated with common pediatric sleep difficulties. Eight domains of sleep, including Bedtime Resistance, Sleep Onset Delay, Sleep Duration, Sleep Anxiety, Night Awakenings, Parasomnias, Sleep Disordered Breathing, and Daytime Sleepiness are assessed, producing eight individual subdomain scores and an overall CSHQ subscore total. CSHQ total score is calculated by adding all the 8 subscores, and ranges from 36 to 108. A higher score is indicative of more disturbed sleep.

End point type	Secondary
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End point timeframe:

Baseline, Day 180, Month 12

End point values	scAAV9.U1a.hS GSH, 3x1013 vg/kg			
Subject group type	Reporting group			
Number of subjects analysed	5 ^[13]			
Units: score on a scale				
arithmetic mean (standard deviation)				
Change from Baseline to Day 180; n=5	2.8 (± 4.76)			
Change from Baseline to Month 12; n=2	1.5 (± 3.54)			

Notes:

[13] - n=participants with an assessment at given time point

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Pediatric Quality of Life Inventory (PedsQL™) Core Generic Scales Total Score

End point title	Change From Baseline in Pediatric Quality of Life Inventory (PedsQL™) Core Generic Scales Total Score
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End point description:

PedsQL is a brief measure of health-related quality of life in children. The Peds QL Generic Core Scales was used in the study, consisting of 23 items applicable for healthy school and community populations, as well as pediatric populations with acute and chronic conditions. The four scales include Physical Functioning, Emotional Functioning, Social Functioning, and School Functioning. Item scores are added

together and averaged to produce a Core total score, where higher scores on a scale of 0-100 indicate better Health-related Quality of Life (HRQOL).

End point type	Secondary
End point timeframe:	
Baseline, Day 180, Month 12	

End point values	scAAV9.U1a.hS GSH, 3x1013 vg/kg			
Subject group type	Reporting group			
Number of subjects analysed	5 ^[14]			
Units: score on a scale				
arithmetic mean (standard deviation)				
Change from Baseline to Day 180; n=5	-11.60 (± 23.218)			
Change from Baseline to Month 12; n=2	-23.80 (± 6.647)			

Notes:

[14] - n=participants with an assessment at given time point

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Parent Quality of Life, Using the Parenting Stress Index, 4th Edition (PSI-4) Total Stress Raw Score

End point title	Change From Baseline in Parent Quality of Life, Using the Parenting Stress Index, 4th Edition (PSI-4) Total Stress Raw Score
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End point description:

The Parenting Stress Index, 4th Edition evaluates the magnitude and type of stress in a parent/child relationship. The short form version was used in the study, consisting of 36 items divided into three domains: Parental Distress (PD), Parent-Child Dysfunctional Interaction (P-CDI), and Difficult Child (DC), which combine together to form a Total Stress raw score. Total Stress raw scores can range from 36 - 180, with higher raw scores indicating higher levels of stress.

End point type	Secondary
End point timeframe:	
Baseline, Day 180, Month 12	

End point values	scAAV9.U1a.hS GSH, 3x1013 vg/kg			
Subject group type	Reporting group			
Number of subjects analysed	5 ^[15]			
Units: score on a scale				
arithmetic mean (standard deviation)				
Change from Baseline to Day 180; n=3	-14.0 (± 24.33)			
Change from Baseline to March 12; n=2	-9.0 (± 4.24)			

Notes:

[15] - n=participants with an assessment at given time point

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Gastrointestinal Symptoms Using the PedsQL™ Gastrointestinal Symptoms Scales Score

End point title	Change in Gastrointestinal Symptoms Using the PedsQL™ Gastrointestinal Symptoms Scales Score
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End point description:

The PedsQL Gastrointestinal Symptoms Scale is a specific module of the PedsQL that measures gastrointestinal symptoms in patients with acute and chronic health conditions as well as healthy school and community populations. The Parent Report version was used on the study, consisting of 58 items across 10 dimensions, assessing parents' perceptions of their child's GI-specific symptoms. Item scores are added together and averaged to produce a GI symptoms scales score, where higher scores on a scale of 0-100 indicate better GI specific QOL.

End point type	Secondary
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End point timeframe:

Baseline, Day 180, Month 12

End point values	scAAV9.U1a.hS GSH, 3x1013 vg/kg			
Subject group type	Reporting group			
Number of subjects analysed	5 ^[16]			
Units: score on a scale				
arithmetic mean (standard deviation)				
Change from Baseline to Day 180; n=4	-5.88 (± 9.261)			
Change from Baseline to Month 12; n=2	-4.15 (± 6.010)			

Notes:

[16] - n=participants with an assessment at given time point

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Parent Global Impression (PGI) Total Score

End point title	Change From Baseline in Parent Global Impression (PGI) Total Score
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End point description:

The Parent Global Impression scale evaluates all aspects of a patients' health and assesses if there has been an improvement or decline in clinical status, as reported by the parent/caregiver. This study used a modified version with symptoms relevant to the patient population in the trial. Nine symptoms were scored at each visit, using a 7-point rating scale where 3 = much better, 2 = better, 1 = slightly better, 0 = same, -1 = slightly worse, -2 = worse, and -3 = much worse. The nine symptom scores are added together to produce a PGI total score, ranging from -27 to 27.

End point type	Secondary
End point timeframe:	
Baseline, Day 180, Month 12	

End point values	scAAV9.U1a.hS GSH, 3x1013 vg/kg			
Subject group type	Reporting group			
Number of subjects analysed	5 ^[17]			
Units: score on a scale				
arithmetic mean (standard deviation)				
Change at Day 180; n=4	-3.0 (± 6.48)			
Change at Month 12; n=3	-3.0 (± 6.56)			

Notes:

[17] - n=participants with an assessment at given time point

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impression Improvement Scale at Day 180 and Month 12

End point title	Clinical Global Impression Improvement Scale at Day 180 and Month 12
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End point description:

The Clinical Global Impression of Improvement scale is a brief, stand-alone assessment of the clinician's view of the patient's global functioning prior to and after initiating a study medication, specifically looking at whether the patient has demonstrated improvement or not. Assessment of improvement was scored at each visit, using a 7-point rating scale where 0 = not assessed, 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse.

End point type	Secondary
End point timeframe:	
Day 180, Month 12	

End point values	scAAV9.U1a.hS GSH, 3x1013 vg/kg			
Subject group type	Reporting group			
Number of subjects analysed	5 ^[18]			
Units: participants				
Global Improvement, Day 180: score=0; n=4	0			
Global Improvement, Day 180: score=1; n=4	0			
Global Improvement, Day 180: score=2; n=4	0			
Global Improvement, Day 180: score=3; n=4	0			
Global Improvement, Day 180: score=4; n=4	1			

Global Improvement, Day 180: score=5; n=4	1			
Global Improvement, Day 180: score=6; n=4	2			
Global Improvement, Day 180: score=7; n=4	0			
Global Improvement, Month 12: score=0; n=3	0			
Global Improvement, Month 12: score=1; n=3	0			
Global Improvement, Month 12: score=2; n=3	0			
Global Improvement, Month 12: score=3; n=3	1			
Global Improvement, Month 12: score=4; n=3	0			
Global Improvement, Month 12: score=5; n=3	0			
Global Improvement, Month 12: score=6; n=3	2			
Global Improvement, Month 12: score=7; n=3	0			

Notes:

[18] - n=participants with an assessment

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Parent Symptoms Score Questionnaire

End point title	Change From Baseline in Parent Symptoms Score Questionnaire
End point description:	
The Parent Symptoms Score Questionnaire contains 29 symptoms with an indicator of whether the symptom was present or absent.	
Due to the inconsistent use of forms across visits and sites for this study, the data collected for this endpoint was incomplete, unreliable, and could not be evaluated.	
End point type	Secondary
End point timeframe:	
Baseline, Day 180, Month 12	

End point values	scAAV9.U1a.hS GSH, 3x10 ¹³ vg/kg			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[19]			
Units: participants				

Notes:

[19] - See explanation in description above for reason this endpoint could not be evaluated.

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Body Mass Index After Treatment

End point title	Percent Change From Baseline in Body Mass Index After Treatment
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End point description:

End point type	Secondary
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End point timeframe:

Baseline, Day 30, Day 180, Month 12

End point values	scAAV9.U1a.hS GSH, 3x1013 vg/kg			
Subject group type	Reporting group			
Number of subjects analysed	5 ^[20]			
Units: percent change				
arithmetic mean (standard deviation)				
Change from Baseline to Day 30; n=4	-0.581 (± 4.4477)			
Change from Baseline to Day 180; n=3	3.875 (± 9.0517)			
Change from Baseline to Month 12; n=2	9.873 (± 6.1672)			

Notes:

[20] - n=participants with an assessment at given time point

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Abnormalities in Standard Awake 45-Minutes-Electroencephalogram (EEG) Monitoring at Baseline and Day 180

End point title	Number of Participants With Abnormalities in Standard Awake 45-Minutes-Electroencephalogram (EEG) Monitoring at Baseline and Day 180
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End point description:

NCS=not clinically significant CS=clinically significant

End point type	Secondary
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End point timeframe:

Baseline, Day 180

End point values	scAAV9.U1a.hS GSH, 3x1013 vg/kg			
Subject group type	Reporting group			
Number of subjects analysed	3 ^[21]			
Units: participants				
Overall EEG : Baseline Abnormal, CS	0			
Overall EEG : Baseline Abnormal, NCS	3			
Overall EEG : Baseline Normal	0			
Overall EEG : Day 180 Abnormal, CS	1			
Overall EEG : Day 180 Abnormal, NCS	1			
Overall EEG : Day 180 Normal	1			

Notes:

[21] - Participants with an assessment

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Vector Shedding Analysis in Plasma, Saliva, Stool and Urine

End point title	Change From Baseline in Vector Shedding Analysis in Plasma, Saliva, Stool and Urine
End point description:	Detection of the adeno-associated Virus 9 (AAV9) viral deoxyribonucleic acid (DNA) in plasma, saliva, urine and feces was analyzed.
End point type	Secondary
End point timeframe:	Baseline, Day 30, Day 180, Month 12

End point values	scAAV9.U1a.hS GSH, 3x1013 vg/kg			
Subject group type	Reporting group			
Number of subjects analysed	5 ^[22]			
Units: Copies per 1 mL of Specimen (copies/mL)				
arithmetic mean (standard deviation)				
Plasma Change from Baseline to Day 30; n=5	45115.0 (± 45413.33)			
Plasma Change from Baseline to Day 180; n=4	-2686.3 (± 5372.50)			
Plasma Change from Baseline to Month 12; n=2	2250.0 (± 3181.98)			
Saliva Change from Baseline to Day 30; n=2	17472.5 (± 18345.89)			
Saliva Change from Baseline to Day 180; n=3	-1900.3 (± 2330.09)			
Saliva Change from Baseline to Month 12; n=1	0.0 (± 99999)			
Stool Change from Baseline to Day 30; n=4	-277522.5 (± 760910.43)			

Stool Change from Baseline to Day 180; n=2	-800833.0 (± 1132548.89)			
Stool Change from Baseline to Month 12; n=1	0.0 (± 99999)			
Urine Change from Baseline to Day 30; n=4	2250.0 (± 2598.08)			
Urine Change from Baseline to Day 180; n=3	1500.0 (± 2598.08)			

Notes:

[22] - n=participants with an assessment at given time point; 99999=not applicable (1 participant analyzed)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All-Cause Mortality: From enrollment to the end of study; mean of 18 months. Adverse Events: from first dose of study drug up to Day 454.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Total
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Reporting group description:

An intravenous injection of ABO-102 (scAAV9.U1a.hSGSH) via peripheral limb vein at a dose of 3.0 x 10¹³ vg/kg

Serious adverse events	Total		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 5 (60.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Foreign body in gastrointestinal tract			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Gastrostomy			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cognitive disorder			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Gait disturbance			

subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Disease progression			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Dysphagia			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Total		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)		
General disorders and administration site conditions			
Gait disturbance			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Rhinitis allergic			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		

Agitation subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Initial insomnia subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Investigations			
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	5 / 5 (100.00%) 11		
Amylase increased subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	3 / 5 (60.00%) 4		
Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all)	3 / 5 (60.00%) 6		
Haematocrit increased subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Blood lactate dehydrogenase increased subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Haemoglobin increased subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Blood creatine phosphokinase increased subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Liver function test increased subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		

Weight increased subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Weight decreased subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Red blood cell count increased subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Platelet count decreased subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
White blood cell count decreased subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Nervous system disorders Ataxia subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Cognitive disorder subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 2		
Epilepsy subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Fine motor skill dysfunction subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Seizure subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Blood and lymphatic system disorders Thrombocytopenia subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Neutropenia			

subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Ear and labyrinth disorders Deafness subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Dysphagia subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1 1 / 5 (20.00%) 1 1 / 5 (20.00%) 1 2 / 5 (40.00%) 2 4 / 5 (80.00%) 5		
Skin and subcutaneous tissue disorders Dermatitis atopic subjects affected / exposed occurrences (all) Ecchymosis subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1 1 / 5 (20.00%) 1		
Endocrine disorders Cushingoid subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Musculoskeletal and connective tissue disorders Bursitis			

subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Synovial cyst			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Myositis			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Musculoskeletal pain			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Oral candidiasis			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Respiratory tract infection			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Otitis media			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Increased appetite			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Hypokalaemia			

subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Decreased appetite			
subjects affected / exposed	3 / 5 (60.00%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 April 2018	- 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: - Screening, Pre-infusion, Days 7, 14, 30, 90, 180, Months 12, 18, 24 visits: Aspartate aminotransferase (AST), alanine transaminase (ALT), serum/plasma gamma-glutamyl transpeptidase (serum/plasma GGT), Serum/plasma total bilirubin - Day 1: Serum/plasma total bilirubin - Days 45, 60, 75, 120, 150, 2-weeks post steroid taper visits: AST, ALT, serum/plasma GGT - Clarified for Screening, Day 30, 180, Month 12 visit regarding abdominal magnetic resonance imaging (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
25 February 2019	- 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 - 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 enzyme replacement therapy (ERT) clinical trial - Deleted exclusion criteria: - Prior treatment with n-sulfoglucosamine sulfohydrolase (SGSH) 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 Pediatric Quality of Life Inventory (PedsQL™), Parenting Stress Index, 4th Edition (PSI-4) and Children's Sleep Habits Questionnaire (CSHQ) clinical questionnaire

25 February 2019	(continued) • Added Sanfilippo Behavior Rating Scale (SBRS) Scales assessment, Parent Global Impression Score, Clinical Global Impression Improvement Scale and Parent Symptom Score Questionnaire • Included diffusion tensor imaging (DTI) analysis on the brain MRI images. • Changed the patient weight for dosing to the one obtained in Screening visit 2. • Included four audiometry clinical assessments (Screening, Month 6, 12 and 24). • Provided more detailed information about the vital sign collection after treatment • Changed some study visit windows to allow more flexibility. • Included new clinical biomarkers such as plasma and CSF cytokines, GM2/GM3. • Added CSF biobanking • Included new gene therapy biomarkers such as neutralizing antibodies against the adeno-associated Virus 9 (AAV9) capsid. • 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 International Conference on Harmonization (ICH) and not all grade 3, 4 or 5. • Replaced terminology of 'subject' with 'participant' • Added 60-minute electroencephalogram (EEG) at Months, 6, 2, 18, and 24
05 March 2020	• 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. • Revised the following secondary outcome to exploratory outcome: • Change from baseline in the Sanfilippo Behavior Rating Scale [Time Frame: Month 6, 12, 18, 24] • Removed brain MRI assessment and brain DTI analysis at Days 30 and 180. • 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. • 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 electroencephalogram (EEG) assessment from 60-minute EEG to 45-minute EEG. • Clarified that audiometry evaluations will start with tympanometry and otoacoustic emissions (OAE). In case relevant alterations are detected, an auditory brainstem response (ABR) along all frequencies will be assessed. • 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 principal investigator (PI).

05 March 2020	(continued) • 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 serious adverse reactions (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 Data Safety Monitoring Board (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. • Clarified the EEG 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.
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported