



Clinical trial results:

ASPIRO: A Phase 1/2, Randomized, Open-Label, Ascending-Dose, Delayed-Treatment Concurrent Control Clinical Study to Evaluate the Safety and Preliminary Efficacy of AT132, an AAV8-Delivered Gene Therapy in X-Linked Myotubular Myopathy (XLMTM) Patients

Summary

EudraCT number	2017-000876-27
Trial protocol	GB DE FR
Global end of trial date	

Results information

Result version number	v1
This version publication date	28 June 2024
First version publication date	28 June 2024

Trial information

Trial identification

Sponsor protocol code	ATX-MTM-002
-----------------------	-------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03199469
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Astellas Pharma Global Development, Inc. (APGD)
Sponsor organisation address	1 Astellas Way Northbrook,, Illinois, United States, 60062
Public contact	Clinical Trial Transparency, Astellas Pharma Global Development, Inc. (APGD), 60062 8008887704, astellas.resultsdisclosure@astellas.com
Scientific contact	Clinical Trial Transparency, Astellas Pharma Global Development, Inc. (APGD), 60062 8008887704, astellas.resultsdisclosure@astellas.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-002571-PIP01-19
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?	Yes

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	30 June 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 September 2021
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the therapeutic dose of resamirigene bilparvovec and to confirm the safety and efficacy of the therapeutic dose of resamirigene bilparvovec

Protection of trial subjects:

This clinical study was written, conducted and reported in accordance with the protocol, International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines, and applicable local regulations, including the European Directive 2001/20/EC, on the protection of human rights, and with the ethical principles that have their origin in the Declaration of Helsinki. Astellas ensures that the use and disclosure of protected health information (PHI) obtained during a research study complies with the federal, national and/or regional legislation related to the privacy and protection of personal information.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 August 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	10 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 7
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	United States: 15
Worldwide total number of subjects	27
EEA total number of subjects	5

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)	14
Children (2-11 years)	13

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:

Participants diagnosed with X-linked myotubular myopathy (XLMTM) resulting from a genetically confirmed mutation in the myotubular myopathy (MTM) 1 gene as assessed by a Sponsor-approved testing facility were enrolled in this study.

Pre-assignment

Screening details:

Participants who met all inclusion criteria and none of the exclusion criteria were enrolled in the study. The study is ongoing, and the data is reported for efficacy Part 1 (week 24) of the study with mortality and safety data being reported up to 5 years. The data cut-off date is 30 June 2023.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	1.3 × 10 ¹⁴ vg/kg (Low dose)

Arm description:

Participants received 1.3 X10¹⁴ viral genomes per kilogram (vg/kg) of body weight resamirigene bilparvovec as a single dose intravenously on Day 1. A sentinel dose was given to first participant and if there were no safety concerns, subsequent participants received either resamirigene bilparvovec at the same dose or control with delayed treatment after at least 4 weeks of post-dose data from the sentinel participant.

Arm type	Experimental
Investigational medicinal product name	Resamirigene bilparvovec
Investigational medicinal product code	AT132
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

All participants received single dose of resamirigene bilparvovec intravenously.

Arm title	3.5 × 10 ¹⁴ vg/kg (High dose)
------------------	--

Arm description:

Participants received 3.5 × 10¹⁴ vg/kg of body weight resamirigene bilparvovec as a single dose intravenously on Day 1. A sentinel dose was given to first participant and if there were no safety concerns, subsequent participants received either resamirigene bilparvovec at the same dose or control with delayed treatment after at least 4 weeks of post-dose data from the sentinel participant.

Arm type	Experimental
Investigational medicinal product name	Resamirigene bilparvovec
Investigational medicinal product code	AT132
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

All participants received single dose of resamirigene bilparvovec intravenously.

Number of subjects in period 1	1.3 × 10¹⁴ vg/kg (Low dose)	3.5 × 10¹⁴ vg/kg (High dose)
Started	7	20
Delayed Treatment Control Group	1	6
Immediate Treatment Group	6	14
Completed	0	0
Not completed	7	20
Adverse event, serious fatal	1	3
Consent withdrawn by subject	1	-
Ongoing	5	14
Randomized, not treated	-	3

Baseline characteristics

Reporting groups

Reporting group title	1.3 × 10 ¹⁴ vg/kg (Low dose)
Reporting group description:	
Participants received 1.3 X10 ¹⁴ viral genomes per kilogram (vg/kg) of body weight resamirigene bilparvovec as a single dose intravenously on Day 1. A sentinel dose was given to first participant and if there were no safety concerns, subsequent participants received either resamirigene bilparvovec at the same dose or control with delayed treatment after at least 4 weeks of post-dose data from the sentinel participant.	
Reporting group title	3.5 × 10 ¹⁴ vg/kg (High dose)
Reporting group description:	
Participants received 3.5 × 10 ¹⁴ vg/kg of body weight resamirigene bilparvovec as a single dose intravenously on Day 1. A sentinel dose was given to first participant and if there were no safety concerns, subsequent participants received either resamirigene bilparvovec at the same dose or control with delayed treatment after at least 4 weeks of post-dose data from the sentinel participant.	

Reporting group values	1.3 × 10 ¹⁴ vg/kg (Low dose)	3.5 × 10 ¹⁴ vg/kg (High dose)	Total
Number of subjects	7	20	27
Age categorical Units:			
Analysis Age at Dosing in Months Units: months			
arithmetic mean	21.78	37.66	
standard deviation	± 15.47	± 24.55	-
Sex Units: Participants			
Male	7	20	27
Female	0	0	0
Analysis Race Units: Subjects			
Asian	0	1	1
Black or African American	0	4	4
Not Reported	0	1	1
White	7	14	21
Ethnicity Units: Subjects			
HISPANIC OR LATINO	3	6	9
NOT HISPANIC OR LATINO	4	13	17
NOT REPORTED	0	1	1
Ventilation Support			
Hours of ventilation support was based on diary data from participants for whom diary data was collected at baseline and by assessment of time off ventilator questionnaire for all other participants. Baseline is defined as average of the diary data values in 7 days leading up to and including day of administration of study drug (i.e. Analysis Day – 6 through Day 1). Full Analysis Set (FAS) population (included all randomized and enrolled participants who received resamirigene bilparvovec and had at least 1 post-dose efficacy assessment) with available data was reported.			
Units: hours			
arithmetic mean	21	23.71	
standard deviation	± 4.69	± 0.52	-

End points

End points reporting groups

Reporting group title	1.3 × 10 ¹⁴ vg/kg (Low dose)
-----------------------	---

Reporting group description:

Participants received 1.3 X10¹⁴ viral genomes per kilogram (vg/kg) of body weight resamirigene bilparvovec as a single dose intravenously on Day 1. A sentinel dose was given to first participant and if there were no safety concerns, subsequent participants received either resamirigene bilparvovec at the same dose or control with delayed treatment after at least 4 weeks of post-dose data from the sentinel participant.

Reporting group title	3.5 × 10 ¹⁴ vg/kg (High dose)
-----------------------	--

Reporting group description:

Participants received 3.5 × 10¹⁴ vg/kg of body weight resamirigene bilparvovec as a single dose intravenously on Day 1. A sentinel dose was given to first participant and if there were no safety concerns, subsequent participants received either resamirigene bilparvovec at the same dose or control with delayed treatment after at least 4 weeks of post-dose data from the sentinel participant.

Primary: Change from Baseline in Hours of Ventilation Support at Week 24

End point title	Change from Baseline in Hours of Ventilation Support at Week 24 ^[1]
-----------------	--

End point description:

The hours of ventilation support were based on diary data from participants for whom diary data was collected at baseline and by assessment of time off ventilator questionnaire for all other participants. Weekly scores were the average of ventilation hours needed for at least 5 out of the 7 days leading up to and including the analysis visit day (e.g., Day 168 for Week 24). For cases where the diary or the ventilator assessment indicated the ventilator type = "None", then zero was imputed for the number of hours on ventilator. FAS population with available data were reported.

End point type	Primary
----------------	---------

End point timeframe:

Baseline, week 24

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: Per protocol, statistical analysis was not planned for this endpoint.

End point values	1.3 × 10 ¹⁴ vg/kg (Low dose)	3.5 × 10 ¹⁴ vg/kg (High dose)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	16		
Units: hours				
arithmetic mean (standard deviation)	-8.92 (± 9.31)	-5.84 (± 5.45)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving Functionally Independent Sitting for At Least 30 seconds by Week 24

End point title	Percentage of Participants Achieving Functionally Independent Sitting for At Least 30 seconds by Week 24
-----------------	--

End point description:

Independence to sit is defined as a participant who sits for at least 30 seconds without assistance from another person or object. Data was determined from the motor milestone electronic case report form (eCRF) or the Bayley Scales of Infant and Toddler Development (BSID) subtest performance criteria number 26, used to determine whether the participant achieves (Yes) or doesn't achieve (No) the milestone. If data was not available then they would be included as "missing". FAS population with available data were reported.

End point type	Secondary
----------------	-----------

End point timeframe:

Week 24

End point values	1.3 × 10 ¹⁴ vg/kg (Low dose)	3.5 × 10 ¹⁴ vg/kg (High dose)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	13		
Units: Percentage of participants				
number (not applicable)				
Achieved	83.3	61.5		
Not Achieved	16.7	38.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reduction in Required Ventilator Support to ≤ 16 Hours a Day from Dosing to Week 24

End point title	Time to Reduction in Required Ventilator Support to ≤ 16 Hours a Day from Dosing to Week 24
-----------------	---

End point description:

The reduced ventilator time was obtained directly from the daily diary or assessment of the time off ventilator questionnaire. The first instance of time reduction reported as ≤ 16 hours per day was considered as an event. Kaplan- Meier (KM) estimate was used for analysis. Here "99999" signifies data was not estimable because less than 50% of participants had event (data was estimated using KM and it requires at least 50% of event to be able to calculate time using KM). FAS population with available data were reported.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline up to week 24

End point values	1.3 × 10 ¹⁴ vg/kg (Low dose)	3.5 × 10 ¹⁴ vg/kg (High dose)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	17		
Units: Weeks				
median (confidence interval 95%)	12.1 (4.1 to 16.1)	99999 (17.1 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) Total Score at Week 24

End point title	Change from Baseline in Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) Total Score at Week 24
-----------------	---

End point description:

The CHOP INTEND is an assessment scale that was originally designed to quantify motor abilities in infants aged 1.4 to 37.9 months, with spinal muscular atrophy type I (SMA-I) and has been validated for X-linked myotubular myopathy (XLMTM). The scale contains 16 questions, each of which is scored on a scale of 0 to 4, with 0 being no response/ability to perform the movement and 4 highest abilities to perform the task, per CHOP INTEND item instructions. The score used for analysis is the total sum of all 16 questions, which will range from 0 to 64. Higher score indicates better neuromuscular function. If an item is missing or scored as "Could Not Test (CNT)" then 0 will be imputed for the item score. FAS population with available data were reported.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline, week 24

End point values	1.3 × 10 ¹⁴ vg/kg (Low dose)	3.5 × 10 ¹⁴ vg/kg (High dose)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	12		
Units: Score on scale				
arithmetic mean (standard deviation)				
Week 24	11.86 (± 15.12)	13.25 (± 13.35)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Maximal Inspiratory Pressure (MIP) at Week 24

End point title	Change from Baseline in Maximal Inspiratory Pressure (MIP) at Week 24
-----------------	---

End point description:

MIP is a quick and non-invasive test to measure strength of inspiratory muscles, primarily diaphragm, and allows for assessment of ventilatory failure, restrictive lung disease and respiratory muscle strength. MIP refers to how much air pressure force an individual creates by inhaling through the mouth as hard as possible. FAS population with available data were reported.

End point type	Secondary
End point timeframe:	
Baseline, week 24	

End point values	1.3 × 10 ¹⁴ vg/kg (Low dose)	3.5 × 10 ¹⁴ vg/kg (High dose)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	12		
Units: centimeter of water (cmH2O)				
arithmetic mean (standard deviation)				
Week 24	41.07 (± 35.03)	26.72 (± 28.35)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Pediatric Quality of Life Inventory (PedsQL) Assessment Total Score at Week 24

End point title	Change from Baseline in Pediatric Quality of Life Inventory (PedsQL) Assessment Total Score at Week 24
-----------------	--

End point description:

PedsQL is a tool designed to measure health-related quality of life in healthy children and adolescents and those with acute and chronic health conditions. PedsQL measures the core dimensions of health as delineated by the World Health Organization, as well as role (school) functioning. This questionnaire has different modules that are administered depending on the age and condition of the child. Each item of the questionnaire is measured on a 5-point likert scale from – 0 (Never) to 4 (Almost always). The module is composed of 25 items comprising 3 dimensions: About My Neuromuscular Disease (17 items), Communication (3 items), About Our Family Resources (5 items). Items are reversed scored and linearly transformed to a total score of 0-100 scale. Higher scales/scores indicate lower problems. FAS population with available data were reported.

End point type	Secondary
End point timeframe:	
Baseline, week 24	

End point values	1.3 × 10 ¹⁴ vg/kg (Low dose)	3.5 × 10 ¹⁴ vg/kg (High dose)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	15		
Units: Score on scale				
arithmetic mean (standard deviation)				
Week 24	9.39 (± 15.51)	12.06 (± 19.23)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Quality of Life Assessment of Caregiver Experience with Neuromuscular Disease (ACEND) Total Score at Week 24

End point title	Change from Baseline in Quality of Life Assessment of Caregiver Experience with Neuromuscular Disease (ACEND) Total Score at Week 24
-----------------	--

End point description:

ACEND was developed to measure impact on parents/legally authorized representatives/caregivers of children with severe neuromuscular disorders. ACEND has 41 items across 2 domains: physical impact [feeding/grooming/dressing {6 items}, sitting/play {5 items}, transfers {5 items} and mobility {7 items} and general caregiver impact {4 items}, emotion {9 items}, and finance {5 items}. Each item is scored on a 6- or 5-point ordinal scale, and scores for each domain and subdomain were scored on 0–100 scale. Higher scores reflected caregivers experiencing less intense care-giving impact. Raw subdomain scores are computed as a mean of completed items, standardized to a 0–100 scale. Higher score indicate better outcomes. FAS population with available data were reported.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline, week 24

End point values	1.3 × 10 ¹⁴ vg/kg (Low dose)	3.5 × 10 ¹⁴ vg/kg (High dose)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	15		
Units: Score on scale				
arithmetic mean (standard deviation)				
Week 24	20.12 (± 18.81)	13.82 (± 12.33)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Quantitative Analysis of Myotubularin Expression in the Muscle Biopsy at Week 24

End point title	Change from Baseline in Quantitative Analysis of Myotubularin Expression in the Muscle Biopsy at Week 24
-----------------	--

End point description:

Myotubularin is a protein, a highly conserved, dual-specific lipid phosphatase that is involved in the development, maturation, and maintenance of skeletal muscle cells. Myotubularin is encoded by an MTM1 gene. FAS population with available data were reported.

End point type	Secondary
End point timeframe:	
Baseline, week 24	

End point values	1.3 × 10 ¹⁴ vg/kg (Low dose)	3.5 × 10 ¹⁴ vg/kg (High dose)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	10		
Units: picograms/well (pg/well)				
arithmetic mean (standard deviation)				
Week 24	923.69 (± 816.09)	2848.40 (± 2903.83)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Percent of Age-appropriate Clinically Relevant Gross Motor Function Milestones Attained Through Week 24

End point title	Mean Percent of Age-appropriate Clinically Relevant Gross Motor Function Milestones Attained Through Week 24
-----------------	--

End point description:

Motor Developmental Milestones included: head control (holds head erect for at least 15 seconds without support), rolls from back to sides (turns from back to both sides), sits without support (sits alone without support for at least 10 seconds), stands with assistance (supports own weight for at least 2 seconds), crawls (makes forward progress of at least 5 feet by crawling on hands and knees), pulls to stand (raises self to standing position using chair or other convenient object for support), walks with assistance (child walks by making coordinated, alternating stepping movements. May hold on with 1 or 2 hands for support), stands alone (stands alone for at least 3 seconds after you release hands), walks alone (takes at least 3 steps without support, even if gait is stiff-legged and wobbly). Mean percentage of gross motor function milestones attained was reported. 99999= not estimable as only 1 participant was analyzed. FAS population with available data were reported.

End point type	Secondary
End point timeframe:	
Baseline, weeks 4, 12, 16 and 24	

End point values	1.3 × 10 ¹⁴ vg/kg (Low dose)	3.5 × 10 ¹⁴ vg/kg (High dose)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	10		
Units: Percentage of gross motor function				
arithmetic mean (standard deviation)				
Baseline (n= 1, 8)	0.0 (± 99999)	12.50 (± 15.81)		
Week 4 (n= 2, 6)	30.00 (± 28.28)	23.33 (± 19.66)		

Week 12 (n= 1, 9)	0.0 (± 99999)	26.85 (± 15.06)		
Week 16 (n= 1, 10)	0.0 (± 99999)	25.25 (± 16.26)		
Week 24 (n= 1, 9)	0.0 (± 99999)	26.67 (± 19.36)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving Full Ventilator Independence at Week 24

End point title	Percentage of Participants Achieving Full Ventilator Independence at Week 24
End point description: "Full ventilator independence" is defined as: the date of removal from ventilator field on the "Assessment of Ventilator Parameters" eCRF is not blank or "Is subject on a ventilator" = "No" on the same eCRF. FAS population with available data were reported.	
End point type	Secondary
End point timeframe: Week 24	

End point values	1.3 × 10 ¹⁴ vg/kg (Low dose)	3.5 × 10 ¹⁴ vg/kg (High dose)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	16		
Units: Percentage of participants				
number (not applicable)				
Achieved	28.6	0.0		
Not Achieved	71.4	100.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Overall Survival

End point title	Duration of Overall Survival
End point description: Survival status was assessed at each visit until the participant withdraws consent or completes the study. If the participant missed a visit or withdraws for a reason other than withdrawal of consent or death, the site contacted the parent(s)/legally authorized representatives to ascertain if the participant was alive. For participants who withdrew from the study, the participant was contacted every 6 months for 5 years after administration and to assess for survival. KM estimate was used for analysis. Here "99999" signifies data was not estimable because less than 50% of participants had event (data was estimated using KM and it requires at least 50% of event to be able to calculate time using KM). FAS population.	

End point type	Secondary
End point timeframe:	
Baseline up to 5 years	

End point values	1.3 × 10 ¹⁴ vg/kg (Low dose)	3.5 × 10 ¹⁴ vg/kg (High dose)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	17		
Units: Months				
median (confidence interval 95%)	99999 (2.10 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with Treatment Emergent Adverse Events (TEAEs)

End point title	Number of participants with Treatment Emergent Adverse Events (TEAEs)
-----------------	---

End point description:

An AE is any untoward medical occurrence in a participant administered a study drug not necessarily having a causal relationship with this treatment. An AE can therefore be any unfavorable & unintended sign, symptom, or disease temporally associated with the use of medicinal product (MP) whether or not considered related to MP. A TEAE is any AEs, regardless of relationship to study drug, that begins or worsens on or after baseline (dosing) visit date. Safety Analysis Set (SAF) consisted of all randomized and/or enrolled participants who received AT132.

End point type	Secondary
End point timeframe:	
From first dose to 5 years	

End point values	1.3 × 10 ¹⁴ vg/kg (Low dose)	3.5 × 10 ¹⁴ vg/kg (High dose)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	17		
Units: Participants				
number (not applicable)	7	17		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose to 5 years

Adverse event reporting additional description:

SAF population

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	v26.0
--------------------	-------

Reporting groups

Reporting group title	1.3 x 10 ¹⁴ vg/kg (Low dose)
-----------------------	---

Reporting group description:

Participants received 1.3 x 10¹⁴ vg/kg of body weight resamirigene bilparvovec as a single dose intravenously on Day 1. A sentinel dose was given to first participant and if there were no safety concerns, subsequent participants received either resamirigene bilparvovec at the same dose or control with delayed treatment after at least 4 weeks of post-dose data from the sentinel participant.

Reporting group title	3.5 x 10 ¹⁴ vg/kg (High dose)
-----------------------	--

Reporting group description:

Participants received 3.5 x 10¹⁴ vg/kg of body weight resamirigene bilparvovec as a single dose intravenously on Day 1. A sentinel dose was given to first participant and if there were no safety concerns, subsequent participants received either resamirigene bilparvovec at the same dose or control with delayed treatment after at least 4 weeks of post-dose data from the sentinel participant.

Serious adverse events	1.3 x 10 ¹⁴ vg/kg (Low dose)	3.5 x 10 ¹⁴ vg/kg (High dose)	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 7 (71.43%)	13 / 17 (76.47%)	
number of deaths (all causes)	1	3	
number of deaths resulting from adverse events	1	3	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cholesteatoma			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Withdrawal hypertension			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			

subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 7 (0.00%)	2 / 17 (11.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Immune system disorders			
Immune system disorder			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epiglottic oedema			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atelectasis			

subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenoidal hypertrophy			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillar hypertrophy			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device dislocation			
subjects affected / exposed	0 / 7 (0.00%)	2 / 17 (11.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Troponin I increased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatine phosphokinase			

increased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Combined immunodeficiency			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocarditis			
subjects affected / exposed	1 / 7 (14.29%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial tachycardia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Seizure			

subjects affected / exposed	1 / 7 (14.29%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Protein-losing gastroenteropathy			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Constipation			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 7 (0.00%)	3 / 17 (17.65%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			

Cholestasis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis cholestatic			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	1 / 7 (14.29%)	2 / 17 (11.76%)	
occurrences causally related to treatment / all	1 / 1	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertransaminasaemia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver disorder			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Joint swelling			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations Pneumocystis jirovecii pneumonia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 7 (0.00%) 0 / 0 0 / 0	1 / 17 (5.88%) 1 / 1 0 / 0	
Bacterial sepsis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 7 (0.00%) 0 / 0 0 / 0	1 / 17 (5.88%) 1 / 1 0 / 0	
Gastroenteritis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 7 (0.00%) 0 / 0 0 / 0	1 / 17 (5.88%) 0 / 1 0 / 0	
Metapneumovirus infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 7 (14.29%) 0 / 1 0 / 0	0 / 17 (0.00%) 0 / 0 0 / 0	
Pneumonia respiratory syncytial viral subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 7 (14.29%) 0 / 1 0 / 0	0 / 17 (0.00%) 0 / 0 0 / 0	
Pneumonia pseudomonal subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 7 (14.29%) 0 / 1 0 / 0	0 / 17 (0.00%) 0 / 0 0 / 0	
Pneumonia parainfluenzae viral subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 7 (14.29%) 0 / 1 0 / 0	0 / 17 (0.00%) 0 / 0 0 / 0	
Pneumonia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 7 (0.00%) 0 / 0 0 / 0	1 / 17 (5.88%) 0 / 1 0 / 0	
Pneumonia viral			

subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 7 (14.29%)	2 / 17 (11.76%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheitis			
subjects affected / exposed	0 / 7 (0.00%)	2 / 17 (11.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Serratia sepsis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Sepsis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Rhinovirus infection			

subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonal sepsis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus bronchiolitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 7 (14.29%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	1.3 x 10 ¹⁴ vg/kg (Low dose)	3.5 x 10 ¹⁴ vg/kg (High dose)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 7 (100.00%)	17 / 17 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cholesteatoma			

subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 17 (5.88%) 2	
Haemangioma of liver subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 17 (5.88%) 1	
Vascular disorders Hypotension subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 17 (5.88%) 2	
Hypertension subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 17 (5.88%) 1	
Surgical and medical procedures Tracheostomy closure subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 17 (0.00%) 0	
General disorders and administration site conditions Hypothermia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 17 (5.88%) 1	
Catheter site extravasation subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 17 (5.88%) 1	
Developmental delay subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 17 (5.88%) 1	
Infusion site extravasation subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 17 (5.88%) 1	
Oedema peripheral subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	3 / 17 (17.65%) 3	
Pain subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 17 (5.88%) 1	
Pyrexia			

subjects affected / exposed occurrences (all)	5 / 7 (71.43%) 9	10 / 17 (58.82%) 14	
Secretion discharge subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 17 (5.88%) 1	
Medical device site granuloma subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 17 (0.00%) 0	
Immune system disorders Allergic oedema subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 17 (0.00%) 0	
Seasonal allergy subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	1 / 17 (5.88%) 1	
Reproductive system and breast disorders Testicular disorder subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 17 (0.00%) 0	
Testicular infarction subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 17 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders Respiratory failure subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 17 (0.00%) 0	
Adenoidal hypertrophy subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 17 (0.00%) 0	
Atelectasis subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 17 (0.00%) 0	
Cough subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	2 / 17 (11.76%) 3	
Epiglottic oedema			

subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	1
Haemoptysis		
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	2
Hypoxia		
subjects affected / exposed	1 / 7 (14.29%)	2 / 17 (11.76%)
occurrences (all)	1	8
Increased bronchial secretion		
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)
occurrences (all)	2	0
Lower respiratory tract inflammation		
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)
occurrences (all)	1	0
Lung infiltration		
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)
occurrences (all)	1	0
Nasal congestion		
subjects affected / exposed	0 / 7 (0.00%)	2 / 17 (11.76%)
occurrences (all)	0	2
Obstructive sleep apnoea syndrome		
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)
occurrences (all)	1	0
Pharyngeal hypertrophy		
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	1
Pleural effusion		
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	1
Productive cough		
subjects affected / exposed	1 / 7 (14.29%)	1 / 17 (5.88%)
occurrences (all)	1	1
Respiratory disorder		
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)
occurrences (all)	1	0
Respiratory tract congestion		

subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Tachypnoea			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Tonsillar hypertrophy			
subjects affected / exposed	1 / 7 (14.29%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Tracheal fistula			
subjects affected / exposed	1 / 7 (14.29%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Upper respiratory tract congestion			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Wheezing			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Rhinorrhoea			
subjects affected / exposed	1 / 7 (14.29%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Autism spectrum disorder			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Insomnia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Sleep disorder			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Product issues			
Device malfunction			

subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Device dislocation			
subjects affected / exposed	1 / 7 (14.29%)	2 / 17 (11.76%)	
occurrences (all)	1	2	
Hepatobiliary disorders			
Biliary dilatation			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Cholelithiasis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences (all)	2	0	
Cholestasis			
subjects affected / exposed	0 / 7 (0.00%)	2 / 17 (11.76%)	
occurrences (all)	0	2	
Gallbladder obstruction			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Hepatic cyst			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Hepatic function abnormal			
subjects affected / exposed	1 / 7 (14.29%)	2 / 17 (11.76%)	
occurrences (all)	1	2	
Hyperbilirubinaemia			
subjects affected / exposed	2 / 7 (28.57%)	6 / 17 (35.29%)	
occurrences (all)	2	6	
Hypertransaminasaemia			
subjects affected / exposed	0 / 7 (0.00%)	2 / 17 (11.76%)	
occurrences (all)	0	3	
Jaundice			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Liver disorder			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences (all)	4	0	

Portal hypertension subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 17 (5.88%) 1	
Investigations			
Activated partial thromboplastin time prolonged subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	3 / 17 (17.65%) 3	
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 2	3 / 17 (17.65%) 3	
Aldolase increased subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 17 (5.88%) 1	
Ammonia increased subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 17 (5.88%) 1	
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	4 / 17 (23.53%) 4	
Bile acids increased subjects affected / exposed occurrences (all)	2 / 7 (28.57%) 2	2 / 17 (11.76%) 3	
Bilirubin urine subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 17 (5.88%) 1	
Blood alkaline phosphatase decreased subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 17 (5.88%) 1	
Human rhinovirus test positive subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 17 (5.88%) 1	
Blood bilirubin increased subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 17 (5.88%) 1	
Blood creatine phosphokinase BB			

increased		
subjects affected / exposed	1 / 7 (14.29%)	1 / 17 (5.88%)
occurrences (all)	1	1
Blood creatine phosphokinase MB increased		
subjects affected / exposed	1 / 7 (14.29%)	3 / 17 (17.65%)
occurrences (all)	1	3
Blood creatine phosphokinase increased		
subjects affected / exposed	5 / 7 (71.43%)	6 / 17 (35.29%)
occurrences (all)	9	7
Blood fibrinogen decreased		
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	1
Blood immunoglobulin G decreased		
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	1
Blood iron increased		
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	1
Blood lactate dehydrogenase increased		
subjects affected / exposed	2 / 7 (28.57%)	2 / 17 (11.76%)
occurrences (all)	2	2
Blood osmolarity increased		
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	1
Blood pressure increased		
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	1
Blood uric acid increased		
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	1
Blood zinc decreased		
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	1
Brain natriuretic peptide increased		

subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	1
C-reactive protein increased		
subjects affected / exposed	3 / 7 (42.86%)	5 / 17 (29.41%)
occurrences (all)	3	6
Carbon dioxide decreased		
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	1
Cardiac imaging procedure abnormal		
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	1
Complement factor decreased		
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)
occurrences (all)	1	0
Cytokine increased		
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)
occurrences (all)	1	0
Echocardiogram abnormal		
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	1
Electrocardiogram QT prolonged		
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)
occurrences (all)	1	0
Electrocardiogram ST segment elevation		
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	1
Electrocardiogram low voltage		
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	1
Faecal fat increased		
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	1
Fibrin D dimer increased		
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	1

Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 7 (28.57%)	3 / 17 (17.65%)	
occurrences (all)	3	3	
Haptoglobin decreased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Heart rate increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	2	
Hepatic enzyme increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Interleukin level increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Ultrasound scan abnormal			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Liver function test abnormal			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Lymphocyte count decreased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	2	
Lymphocyte count increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Lymphocyte morphology abnormal			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Myocardial necrosis marker increased			

subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	1
Neutrophil toxic granulation present		
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	1
Occult blood positive		
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	1
Oxygen saturation decreased		
subjects affected / exposed	1 / 7 (14.29%)	1 / 17 (5.88%)
occurrences (all)	1	2
Pancreatic enzymes increased		
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)
occurrences (all)	1	0
Platelet count decreased		
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)
occurrences (all)	1	0
Prealbumin decreased		
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	1
Protein total decreased		
subjects affected / exposed	2 / 7 (28.57%)	0 / 17 (0.00%)
occurrences (all)	3	0
Prothrombin time abnormal		
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	1
Prothrombin time prolonged		
subjects affected / exposed	0 / 7 (0.00%)	2 / 17 (11.76%)
occurrences (all)	0	2
QRS axis abnormal		
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)
occurrences (all)	1	0
Red blood cell burr cells present		
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	1
Red blood cell count decreased		

subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	1
SARS-CoV-2 test positive		
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	1
Serum ferritin increased		
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	1
Stool reducing substances increased		
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	1
Thrombin time prolonged		
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	1
Transaminases increased		
subjects affected / exposed	3 / 7 (42.86%)	3 / 17 (17.65%)
occurrences (all)	3	4
Transferrin decreased		
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	1
Transferrin saturation increased		
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	1
Troponin I increased		
subjects affected / exposed	1 / 7 (14.29%)	2 / 17 (11.76%)
occurrences (all)	2	4
Troponin T increased		
subjects affected / exposed	1 / 7 (14.29%)	5 / 17 (29.41%)
occurrences (all)	2	6
Troponin increased		
subjects affected / exposed	1 / 7 (14.29%)	2 / 17 (11.76%)
occurrences (all)	1	2
Ultrasound liver abnormal		
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)
occurrences (all)	1	0
Interleukin-2 receptor increased		

subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Urine sodium decreased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
White blood cell count decreased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
White blood cell count increased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Weight decreased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Craniocerebral injury			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Facial bones fracture			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Fall			
subjects affected / exposed	2 / 7 (28.57%)	4 / 17 (23.53%)	
occurrences (all)	3	5	
Head injury			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Humerus fracture			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Infusion related reaction			

subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Post procedural complication			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Post procedural fever			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Radius fracture			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Skin abrasion			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Stoma complication			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Stoma site hypergranulation			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Tibia fracture			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Upper limb fracture			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Vaccination complication			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	2	
Congenital, familial and genetic disorders			
Dolichocephaly			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Laryngeal cleft			

subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 17 (0.00%) 0	
Talipes subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 17 (0.00%) 0	
Portal venous system anomaly subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 17 (5.88%) 1	
Cardiac disorders			
Bradycardia subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 17 (0.00%) 0	
Bundle branch block right subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 17 (0.00%) 0	
Coronary sinus dilatation subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 17 (0.00%) 0	
Left ventricular hypertrophy subjects affected / exposed occurrences (all)	2 / 7 (28.57%) 2	0 / 17 (0.00%) 0	
Mitral valve incompetence subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 17 (0.00%) 0	
Myocarditis subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 17 (5.88%) 1	
Pulmonary valve incompetence subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 17 (0.00%) 0	
Right ventricular dysfunction subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 17 (0.00%) 0	
Sinus bradycardia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 17 (5.88%) 1	

Sinus tachycardia subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	1 / 17 (5.88%) 1	
Tachycardia subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	1 / 17 (5.88%) 1	
Tricuspid valve incompetence subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 17 (0.00%) 0	
Nervous system disorders Seizure subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 2	1 / 17 (5.88%) 1	
Language disorder subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 17 (5.88%) 1	
Tremor subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 17 (5.88%) 1	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 17 (5.88%) 4	
Immune thrombocytopenia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 17 (5.88%) 1	
Iron deficiency anaemia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 17 (5.88%) 1	
Leukocytosis subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	1 / 17 (5.88%) 1	
Leukopenia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 17 (5.88%) 1	
Lymphopenia			

subjects affected / exposed	1 / 7 (14.29%)	1 / 17 (5.88%)	
occurrences (all)	2	1	
Neutropenia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Neutrophilia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Splenomegaly			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Thrombocytopenia			
subjects affected / exposed	2 / 7 (28.57%)	9 / 17 (52.94%)	
occurrences (all)	2	11	
Thrombocytosis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Coagulopathy			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Ear discomfort			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Hypoacusis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	2	
Otorrhoea			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Astigmatism			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Dry eye			

subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 17 (5.88%) 1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Abdominal pain upper			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Anal fissure			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Ascites			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Constipation			
subjects affected / exposed	2 / 7 (28.57%)	6 / 17 (35.29%)	
occurrences (all)	2	9	
Diarrhoea			
subjects affected / exposed	3 / 7 (42.86%)	3 / 17 (17.65%)	
occurrences (all)	8	7	
Dyspepsia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Epigastric discomfort			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Gastritis			
subjects affected / exposed	1 / 7 (14.29%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	

Ileus			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Impaired gastric emptying			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	0 / 7 (0.00%)	2 / 17 (11.76%)	
occurrences (all)	0	2	
Regurgitation			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Salivary hypersecretion			
subjects affected / exposed	1 / 7 (14.29%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Teething			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	1 / 7 (14.29%)	9 / 17 (52.94%)	
occurrences (all)	3	13	
Skin and subcutaneous tissue disorders			
Acanthosis nigricans			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Dermatitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Dermatitis diaper			
subjects affected / exposed	0 / 7 (0.00%)	2 / 17 (11.76%)	
occurrences (all)	0	2	
Drug eruption			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Erythema			

subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Hirsutism			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Pigmentation disorder			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Pruritus			
subjects affected / exposed	1 / 7 (14.29%)	2 / 17 (11.76%)	
occurrences (all)	1	3	
Rash			
subjects affected / exposed	1 / 7 (14.29%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Rash erythematous			
subjects affected / exposed	0 / 7 (0.00%)	2 / 17 (11.76%)	
occurrences (all)	0	2	
Skin disorder			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Urticaria			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Haematuria			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Proteinuria			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Renal cyst			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences (all)	1	0	

Urinary retention subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 17 (5.88%) 1	
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 17 (5.88%) 1	
Precocious puberty subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	1 / 17 (5.88%) 1	
Musculoskeletal and connective tissue disorders Epiphyses delayed fusion subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 17 (0.00%) 0	
Epiphyses premature fusion subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	1 / 17 (5.88%) 1	
Extremity contracture subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 17 (5.88%) 1	
Kyphosis subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 17 (0.00%) 0	
Myositis subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 17 (5.88%) 1	
Osteopenia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	2 / 17 (11.76%) 2	
Pain in extremity subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 17 (5.88%) 1	
Scoliosis subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 17 (0.00%) 0	
Synovial cyst			

subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 17 (0.00%) 0	
Infections and infestations			
Cystitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Adenovirus infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Atypical pneumonia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Bacterial tracheitis			
subjects affected / exposed	2 / 7 (28.57%)	2 / 17 (11.76%)	
occurrences (all)	2	6	
Bacteriuria			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Bronchiolitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Bronchitis			
subjects affected / exposed	1 / 7 (14.29%)	2 / 17 (11.76%)	
occurrences (all)	1	2	
COVID-19			
subjects affected / exposed	2 / 7 (28.57%)	4 / 17 (23.53%)	
occurrences (all)	2	4	
Candida infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Catheter site infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Clostridium difficile infection			
subjects affected / exposed	0 / 7 (0.00%)	2 / 17 (11.76%)	
occurrences (all)	0	2	

Conjunctivitis		
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	1
Coxsackie viral infection		
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)
occurrences (all)	1	0
Ear infection		
subjects affected / exposed	0 / 7 (0.00%)	2 / 17 (11.76%)
occurrences (all)	0	2
Rhinovirus infection		
subjects affected / exposed	1 / 7 (14.29%)	1 / 17 (5.88%)
occurrences (all)	1	2
Enterobiasis		
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)
occurrences (all)	1	0
Gastroenteritis viral		
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	1
Gastrointestinal bacterial infection		
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	1
Gastrointestinal bacterial overgrowth		
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)
occurrences (all)	1	0
Gastrointestinal viral infection		
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)
occurrences (all)	1	0
Hand-foot-and-mouth disease		
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	1
Influenza		
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	1
Lower respiratory tract infection		
subjects affected / exposed	0 / 7 (0.00%)	2 / 17 (11.76%)
occurrences (all)	0	2

Metapneumovirus infection		
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	1
Nasopharyngitis		
subjects affected / exposed	1 / 7 (14.29%)	2 / 17 (11.76%)
occurrences (all)	2	4
Onychomycosis		
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	1
Oral candidiasis		
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	1
Otitis externa		
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)
occurrences (all)	2	0
Otitis media		
subjects affected / exposed	4 / 7 (57.14%)	4 / 17 (23.53%)
occurrences (all)	7	5
Otitis media acute		
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	1
Otitis media staphylococcal		
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)
occurrences (all)	1	0
Pharyngitis		
subjects affected / exposed	0 / 7 (0.00%)	2 / 17 (11.76%)
occurrences (all)	0	2
Pneumonia		
subjects affected / exposed	1 / 7 (14.29%)	1 / 17 (5.88%)
occurrences (all)	2	1
Pneumonia aspiration		
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)
occurrences (all)	1	0
Pneumonia pneumococcal		
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)
occurrences (all)	1	0

Pseudomonas infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Rectal abscess			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Respiratory syncytial virus bronchiolitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 7 (0.00%)	3 / 17 (17.65%)	
occurrences (all)	0	4	
Respiratory tract infection			
subjects affected / exposed	0 / 7 (0.00%)	3 / 17 (17.65%)	
occurrences (all)	0	3	
Respiratory tract infection bacterial			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Rhinitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	2	
Ear infection staphylococcal			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Scarlet fever			
subjects affected / exposed	0 / 7 (0.00%)	2 / 17 (11.76%)	
occurrences (all)	0	2	
Skin candida			
subjects affected / exposed	0 / 7 (0.00%)	2 / 17 (11.76%)	
occurrences (all)	0	2	
Tracheitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	4	
Tracheostomy infection			

subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	3 / 7 (42.86%)	7 / 17 (41.18%)	
occurrences (all)	6	15	
Upper respiratory tract infection bacterial			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Urinary tract infection bacterial			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Viral upper respiratory tract infection			
subjects affected / exposed	4 / 7 (57.14%)	5 / 17 (29.41%)	
occurrences (all)	9	7	
Metabolism and nutrition disorders			
Feeding intolerance			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Hypercholesterolaemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Hyperkalaemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	2	
Hypernatraemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Hypertriglyceridaemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Hyperuricaemia			
subjects affected / exposed	2 / 7 (28.57%)	1 / 17 (5.88%)	
occurrences (all)	2	1	
Hypoalbuminaemia			

subjects affected / exposed	1 / 7 (14.29%)	2 / 17 (11.76%)	
occurrences (all)	2	2	
Hypochloraemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Hypokalaemia			
subjects affected / exposed	0 / 7 (0.00%)	3 / 17 (17.65%)	
occurrences (all)	0	4	
Hypomagnesaemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Hyponatraemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	2	
Hypophosphataemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Vitamin A deficiency			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Vitamin D deficiency			
subjects affected / exposed	0 / 7 (0.00%)	2 / 17 (11.76%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 June 2017	• The first subject in Cohorts 1, 2, and 3 will be assigned to active treatment. Subsequent subjects in each cohort will be randomized (2:1) to active or control (delayed-treatment). • Increased allowed AAV8 neutralizing antibody titer level to 1:20; delete exclusion based on total AAV8 antibody titer. • Added blood draw for baseline PBMC assessment at the Muscle Biopsy time point. • Added collection of viral shedding samples to Weeks 1, 2, 3, 5, 6, 7, and 8. Sampling will continue until three consecutive data points at or below the limit of detection (LOD) are collected from any one of the sample types. • Added the option of performing Week 3, 5, 6, and 7 visits in the study site clinic or at home. • Changed "stool" to "rectal swab" when describing how to obtain sample for viral shedding. • Revised steroid withdrawal language to allow for greater investigator discretion. • Added replacement of subjects who withdraw prior to Week 48. • Resolved conflict between protocol & muscle biopsy manual re preferred location of sampling: protocol states 1) vastus lateralis; 2) gastrocnemius. Muscle biopsy manual states 1) left gastrocnemius; 2) right gastrocnemius; 3) vastus lateralis (either side). • Resolved conflict between protocol & ICF: biological samples must be labelled w/subject's initials (protocol); will not be labelled w/subject's initials (ICF). • Added that the PedsQL will be used for children < 2 years of age. • Deleted requirement for pediatric cardiologist to review all ECGs and ECHOs. Revise text to require pediatric cardiologist to review ECGs and/or ECHOs if abnormal, in order to determine clinical significance. • Added "Control" to the name of each visit in the control phase of the study. • Clarified Control period AEs vs AEs that occur after treatment with AT132. • Excluded Therapies language was modified to match that used in VALENS. • Statistics sections have been updated & revised by new statistician.
14 June 2017	• Deleted Day 0. • Corrected typographical and grammatical errors, errors discovered during a QC check of the document (including references), inconsistencies in text between documents.

25 January 2018	• Clarified criteria for selection of optimal dose. • Extended glucocorticoid therapy period to 8 weeks, then tapering from the original dose over 8 weeks. • Added information regarding use of supplemental intravenous steroids or other immunosuppressive regimens in cases of potential malabsorption of oral medications, or in response to liver or cardiac enzyme elevations, or in response to suspected myositis. • Added Exclusion Criterion: "Subject has a contraindication to prednisolone." • Added Exclusion Criterion: "Subject has a contraindication to study drug or ingredients." • Additional information regarding IMP storage. • Added information regarding lab values to monitor during steroid taper. • Clarified the total amount of blood to be drawn over an 8-week period of study participation (70 mL) as local labs will be available quickly, Safety lab tests drawn immediately before dosing and through Week 16 will be processed at each study site's local lab, while other lab tests will be processed at the Central Lab. • Weaning from invasive or noninvasive ventilatory support will be conducted in collaboration with each subject's pulmonologist. Consideration should be given to performing a sleep study before weaning a subject fully off of ventilatory support. • Removed total Anti-AAV8 antibody testing. • Based on DMC recommendations following safety information collected from the first three subjects enrolled following changes were made: - o Added Anti-AAV8 and Anti-MTM1 Antibodies to Week 1, Week 4, and Week 16 Visits. - o Added PBMCs to Week 1, Week 4, Week 6, and Week 8 Visits. - o Added Week 9, 10, 11, 13, 14, and 15 Visits. - o Added Week 16 Visit. • Administrative changes made for corrections, consistency, clarity. • Updated AveXis and Beggs, Byrne references. • Corrected error in CGIS scoring. "Not assessed" is not assigned a score. Hence deleted score "0".
21 November 2018	• Updated the requirement to use local or the central lab for safety laboratory tests to all for more flexibility. • Added assessment for Platelet Analysis at Baseline, Day 2, Day 4, Day 6, Week 1, and Week 2 to allow for improved monitoring of transient platelet count which decreases during the first week post dosing. • Clarify the analyses being conducted with the muscle biopsies. • Updated the method of collection to stool sample collection. • Updated maximum blood sample volume to account for the addition of platelet analyses in the blood sample volume estimate. • To provide specific immunosuppression guidance for the treatment of myocarditis • Include CK isoenzymes into the serum chemistry panel to improve CK monitoring. • To improve safety monitoring: - o Added requirement to conduct cardiac magnetic resonance imaging in cases of increased troponin I and ECG/ECHO changes in cases suggestive of myocarditis. - o Add ECHO assessment at Week 12 visit. • Administrative changes made for corrections, consistency, clarity.
01 May 2019	• Study was expanded to evaluate efficacy in greater number of patients. • The objectives were changed to align with the modification of the study to include Part 2 to determine the safety and efficacy of the optimal dose of AT132. • Following feedback from the regulatory authorities in the USA and EU: - o The efficacy endpoints were modified. The endpoints were selected to represent clinically relevant assessments for patients with XLMTM. - o ASPIRO was modified into 2 parts. Part 1 was designed to determine the optimal dose, and Part 2 includes an additional cohort of subjects in which the safety and efficacy of AT132 will be evaluated with clinically relevant endpoints. - o specific guidelines for the requirements prior to the initiation of ventilator weaning were included in the protocol. • The ventilatory dependency for subjects in Part 2 was added. • The exclusion criteria were modified: - o For clarity. - o To include additional criteria for the new Part 2 of the study. These criteria were selected to align with the new efficacy endpoints selected for the study. • Study design was modified for clarification purposes. • Timing was adjusted in line with current study design. • "Review of important medical events" text was added to reflect the current DMC charter. • Statistical methods were updated to clarify the analyses that will be conducted for Part 1 and Part 2. • The Investigator's Brochure has been updated during ASPIRO. • Text added to subject identification. • Duration of study participation was changed for accuracy • The Method of Assigning Subjects to Treatment Groups was modified. • The description of the blinding was modified for clarity around the blinding of the study. • Requirement to return unused AT132 removed. • Text included to provide instructions for subjects weighing ≥ 60 kg.

01 May 2019	• Text was added to describe the diagnosis, treatment, and adjudication of elevations in cardiac enzymes. • Text was included for clarity around the use of physical therapy in the management of subjects with XLMTM. • Text was added for clarity around capturing medical history information. • Human Leukocyte Antigen (HLA) Testing was added to study the association of potential AEs with particular HLA alleles. • Text was added to include specific cytokine profile that should be assessed prior to administration of AT132. • Description of the Parental Swallowing Questionnaire, description of Speech Development Parental Questionnaire and Communicative Development Inventories, description of EQ-5D, description of In Depth Interviews of Caregivers and Subjects were added. • Section on Hospitalization Rate and Length of Stay to describe this new secondary efficacy endpoint for ASPIRO. The schedule of study events is now in text rather than as an appendix for easy understanding of Schedule of assessments given in table format. • The MFM-20 was replaced with the MFM-32. • Revised details around the assessment of ventilator requirements using a polysomnogram. • Revised details around the implementation of an electronic diary to record ventilator dependence has been added. • Text was added regarding LAR for clarity. • Text was removed regarding the assessment of sprinting. • Text was added to describe the new endpoint of the assessment of annualized respiratory hospitalization rate. • Text was added for clarity regarding the new endpoints for ASPIRO. • A section titled "Motor Developmental Milestones" was added in line with the modification of the secondary efficacy endpoints following communications with the USA and EU regulatory authorities. • Bayley III scales section was moved up as assessments were reordered.
01 May 2019	• Text describing that the validation of the CHOP INTEND has been published. • Description of ACTIVE was removed as it is no longer required as this assessment has been removed from ASPIRO. • Description of vocalization assessments was removed. • Platelet monitoring text was modified to remove requirement that assessment was done during the first 2 weeks following study drug administration to reduce blood volume requirements. • Schedule of events added as a table. • Footnotes updated throughout. Included as a table to improve ease of reading. • Schedule of events was updated with revised collection times for viral shedding. • Anti-MTM1 antibody analysis removed for control subjects. • Section renamed "SAE Onset and Resolution Dates. Text was modified to provide clarification around criteria to establish the length of the SAE. • Statistical considerations section was rewritten.
08 October 2019	• Elevated secondary endpoint to key secondary endpoint. • Clarification of the Part 2 endpoint objective • Indication of Inclusion and exclusion criteria that will apply to the delayed treatment control subjects when they transition to the treatment arm. • Explanation of optimal dose determination to define the optimal dose determined by the data monitoring committee and sponsor. • Clarification of control subject procedures and transition to treatment. • Updated study design graphic. • Corrected time points for primary efficacy endpoint analysis. • Clarification of Dose Selection Rationale. • Added optimal dose explanation and rationale. • Clarification of treatment recommendation for Severe Myocarditis events. • Added interferon (IFN)-γ and tumor necrosis factor (TNF) α to list of cytokine profile parameters. • Stopping criteria for PSG was updated. • W24 PSG to require a longer PSG at W24 compared to the Baseline PSG was updated, and W48 PSG was added. • Text added to explain that the in-depth interviews are only optional. • Fixed SOE table to indicate urinalysis collection • Ventilator Weaning and Discontinuation Assessment for Control visits was added to align with treatment arm assessments. • Control W24 visit window was updated to be consistent with the treatment arm window and allow more flexibility for scheduling. • Requirement for laboratory abnormalities of interest to be reported as AEs regardless of clinical significance was added to capture laboratory abnormalities of interest as AEs. • Text to define how growth parameters will be analyzed was added for clarity. • Study stopping criteria for neuromuscular and cardiac AEs possibly related or related to AT132 was updated to clarify stopping criteria description to support appropriate safety monitoring.

07 April 2020	• Updated Study Phase To align the clinical trial phase with the confirmatory nature of the investigation • Updated acronyms for consistency • Modified glucocorticoid therapy for accuracy. Number of participants changed to reflect the number of subjects enrolled in Part 2. • Administrative changes made for corrections, consistency, clarity and accuracy. Included Pulmonary Adjudication Committee for completeness. • Modifications made to align with IB. Modifications in objectives wording to align with objectives in synopsis Text moved and modified to align with Sponsor protocol template and consistency across studies. • Modifications made for alignment with Ventilation Manual information. • Modifications to align with the muscle biopsy charter. • Equivalent forms were added and removed financial disclosure form numbers. • Updates made to align with ICMJE
16 November 2020	• Reflected the latest risk evaluation and available information due to safety findings which are likely to impact the risk/benefit assessment. • Text modification for clarification on age limit and glucocorticoid use. • Last study visit extended to allow for additional follow-up. • Administrative changes made for corrections, consistency, clarity. • Text modification in necessary sections for clarification on which exclusion criteria should be met. • Text modification in necessary sections to describe the decision-making process, historically and currently, for choosing each dose level. • Text modification in necessary sections to account for time untreated delayed-treatment control subjects may have to wait to be treated due to study delays. • Text modification in necessary sections to reflect the status of each part of the study and describe how Part 2 subjects will be treated going forward; to reduce redundancy with the description of Part 2 elsewhere in the synopsis. • Text modification in necessary sections to align with the CAC Charter. • Text correction in necessary sections to align with primary endpoint and updated language to reflect planned analyses based on current enrollment. • Text modification for alignment with IB v7. • Instructions for use of glucocorticoids consolidated in necessary sections. • Text added to describe how potential new subjects may be enrolled. • Text added to provide guidance for enrolled subjects who are deemed ineligible for treatment but want to remain in the study. • As dose selection rationale was consolidated text was modified in sections for consistency. • Reorganized text related to immunosuppressive treatments for clarity and to remove redundancy. • Added new section for mitigation of possible cholestasis-related liver injury.

16 November 2020	• Added new section - o To consolidate information related to cardiac and hepatic safety events. - o To describe notification and consultative parameters to assist investigators and/or other clinicians involved in the care of study subjects and to identify clinically significant abnormalities during routine cardiac monitoring. - o To clarify and give specific guidance to the clinical site on how to monitor for and manage any case of suspected myocarditis or potential hepatobiliary toxicity. • Text modified to remove contradiction to other immunosuppressive medications. • Text modified to provide guidance to sites on steps to take when assessments cannot be conducted as planned. • Text modified to complement monitoring and additional cytokine monitoring were added upon request of a regulatory agency to help assess possible immune responses, including innate immune responses, following AT132 administration. • Text modified for alignment with data collected on the CRF. • Text added for TAb test to evaluate post-dose immune responses. • Site information removed which was available in previous sections. • Text added for alignment with the Guidance for Industry: Long Term Follow-Up After Administration of Human Gene Therapy Products (FDA, 2020) • Added text for complement testing to aid in monitoring of possible innate immune responses after AT132 administration. • Serum Bile Acid Assay added as an exploratory measure to possibly aid in better understanding of cholestatic events in XLMTM. • Section for Nasobiliary drainage was added. • Section for Transient Elastography of the Liver by Ultrasound was added as an exploratory measure to possibly aid in better understanding of cholestatic events in XLMTM. • Schedule of events updated for screening visit and week 8 to align with protocol.
16 November 2020	• Schedule of events updated with minor corrections and to align with protocol for EOS (week 9 to month 60 and control baseline and control month 30). • New section of Assessments for Untreated Delayed-Treatment Control Subjects added to allow for additional follow-up on enrolled subjects who are deemed ineligible for treatment but want to remain in the study. • Text modified and deleted to consolidate, remove any redundancy, and point the reader to the newly created section containing the details about how to handle cardiac enzyme elevations. • New section added of Hyperbilirubinemia for alignment with IB v7. • Text modified to reflect planned analyses based on current enrollment. • Text correction for primary endpoint to align with primary endpoint and added language to reflect planned analysis populations based on current enrollment. • Text modified for alignment with the populations to be assessed in the study. • List was updated to ensure that a hepatobiliary AE of Grade ≥ 3 would be trigger the stopping criteria. Although the new criterion is redundant with the first stopping criterion, by creating a separate bullet, it is felt that better focus and attention is drawn to the most concerning safety event seen thus far. • Section updated to align with conservative global retention policies.

15 January 2021	• Changed dose of AT132 as determined by the 2nd generation vg titer assay. • Explanation added on how the doses were determined. • Administrative changes made for corrections, consistency, clarity. • The 2nd generation vg titer assay was used moving forward when dosing subjects on this study. • Description on the decision to move forward with the therapeutic dose after recharacterization of historical lots previously administered to the lower dose level group using the 2nd generation vg titer assay. • Text added to document receipt of SARS-CoV-2 vaccination in the clinical study record, given the emergency authorization of various vaccines and limited understanding of potential long-term vaccine-related adverse events and to provide guidance to investigators regarding vaccination administration in corticosteroid-treated patients, particularly in light of developments related to SARS-CoV-2. • Text modified to allow a process for determining if investigational treatments not related to XLMTM may be used. • Modified section to allow for collection of retrospective documentation to support adjudication for these subjects, as the adjudication process and committee were implemented subsequent to discontinuation of their ventilatory support and to support independent, expert, retrospective evaluation of their readiness to discontinue this support. • Modified section to allow for collection of retrospective documentation to support adjudication for these subjects, as their baseline evaluations were performed prior to implementation of a prospective process for motor milestone acquisition adjudication and to support independent, expert, retrospective evaluation of their baseline status. • Added Ventilator Weaning and Discontinuation Assessment to align with timepoints and footnote for treated subjects.
15 January 2021	• Deleted "A single blood sample can be drawn for assays of anti-AAV8 antibodies and anti-MTM1 antibody." from sections to prevent potential contradictory instructions in Laboratory Manual.
03 February 2022	• Administrative changes made for corrections, consistency, clarity • Text modified to include follow-up beyond year 5 and through year 10. • Footnotes updated to bring the figure into alignment as this protocol amendment does not allow for enrollment or dosing of new subjects. • Abbreviations added for completeness. • Text modified to provide updated safety data and the data cutoff date for assessment. • Added text to provide reference for the timing of risk evaluation. • Modified text to better understand the long-term behavior of intrahepatic cholestasis in XLMTM subjects in necessary sections. • Added text to clarify the involvement of the site hepatologist to enhance subject safety. • Modified text to align with the current procedure. • Modified text to clarify the safety reporting process to enhance subject safety in necessary sections. • Administrative change for consistency and accuracy. • Administrative; to report the change of the Sponsor's Medical Director and Head of Regulatory Affairs.

16 May 2023	• Revised synopsis to update the endpoints based on the current enrollment, dosing and collected data. • Revised synopsis and its sections to: - o clarify estimands for this study. - o reflect the status of study. - o incorporate country-specific items into global protocol. - o remove 3 independent adjudication committees based on the status of study. - o reflect planned analyses based on the current enrollment and dosing. • Abbreviations added for completeness. • Administrative changes made for corrections, consistency, clarity. • Added text to reflect the status of study. • Added text to reflect the latest risk evaluations. • Modified text in sections to reflect the status of study. • Modified sections to remove 3 independent adjudication committees based on the status of study. • Revised sections to incorporate country-specific items into global protocol. • Revised sections to reflect the currently available safety information. • Modified text to allow for further assessments of treatment effect with genome sequencing in the future. • Deleted section to remove EQ-5D series due to limitations of collected data. • Modified section to allow for further assessments of immune cells with flow cytometry. • Revised section to reduce burden of subjects for 10- year follow-up assessments. • Reflected the latest risk evaluation and available information due to safety findings which are likely to impact the risk/benefit assessment. - o incorporate country-specific items into global protocol. - o remove 3 independent adjudication committees based on the status of study. - o reflect planned analyses based on the current enrollment and dosing. - Abbreviations added for completeness. • Administrative changes made for corrections, consistency, clarity.
16 May 2023	• Added text to reflect the status of study. • Added text to reflect the latest risk evaluations. • Modified text in sections to reflect the status of study. • Modified sections to remove 3 independent adjudication committees based on the status of study. • Revised sections to incorporate country-specific items into global protocol. • Revised sections to reflect the currently available safety information. • Modified text to allow for further assessments of treatment effect with genome sequencing in the future. • Deleted section to remove EQ-5D series due to limitations of collected data. • Modified section to allow for further assessments of immune cells with flow cytometry. • Revised section to reduce burden of subjects for 10- year follow-up assessments. • Reflected the latest risk evaluation and available information due to safety findings which are likely to impact the risk/benefit assessment. • Updated the endpoints based on the nature and limitations of the collected data. • Revised section to collect subject's data as much as possible after the study withdrawal. • Modified text to clarify the safety reporting process on severe hepatic liver function abnormalities. • Modified text in necessary sections to reflect planned analyses based on the current enrollment and dosing. • Addition in Appendix to allow for further assessments of treatment effect with genome sequencing in the future.

17 May 2024	• Administrative changes made for corrections, consistency, clarity. • Modified sections to reflect the latest risk evaluation and available information. • Revised sections to update the monitoring and management plan for safety events based on the latest safety information. • Revised sections to streamline the efficacy assessment in the long-term follow-up period. • Revised sections to add a recommended assessment/testing for safety events based on the latest safety information. • Revised sections to update the study assessments accordingly with changes to the management plan for safety events. • Revised sections to capture necessary efficacy data in the long-term follow-up period (Years 6 and 10).
-------------	--

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported