



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 | v2 |
| This version publication date | 28 September 2024 |
| First version publication date | 28 June 2024 |
| Version creation reason | |

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 | Safety, Efficacy |
| 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 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. | |

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 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 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 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. The concentration of the sample was normalized such that the equivalent amount of protein was tested per sample. 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 (pg) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 24 | 923.69 (± 816.09) | 2848.40 (± 2903.83) | | |

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 5point 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 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: 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:

All-cause mortality and AEs included SAF population that consisted of all randomized participants who received resamirigene bilparvovec.

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

Dictionary used

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

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

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | 3.5 x 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.

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

Reporting group description:

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

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

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

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

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

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

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

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

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 7 (14.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory syncytial virus infection | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pseudomonal sepsis | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory syncytial virus bronchiolitis | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 7 (14.29%) | |
| 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 | 3.5 x 10 ¹⁴ vg/kg (High dose) | 1.3 x 10 ¹⁴ vg/kg (Low dose) | |
|---|---|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 17 / 17 (100.00%) | 7 / 7 (100.00%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Cholesteatoma | | | |

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

| | | | |
|--|-----------------------------------|--------------------------------|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>1 / 17 (5.88%)</p> <p>1</p> | <p>0 / 7 (0.00%)</p> <p>0</p> | |
| <p>Pyrexia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>10 / 17 (58.82%)</p> <p>14</p> | <p>5 / 7 (71.43%)</p> <p>9</p> | |
| <p>Secretion discharge</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>1 / 17 (5.88%)</p> <p>1</p> | <p>0 / 7 (0.00%)</p> <p>0</p> | |
| <p>Immune system disorders</p> <p>Allergic oedema</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>0 / 17 (0.00%)</p> <p>0</p> | <p>1 / 7 (14.29%)</p> <p>1</p> | |
| <p>Seasonal allergy</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>1 / 17 (5.88%)</p> <p>1</p> | <p>1 / 7 (14.29%)</p> <p>1</p> | |
| <p>Reproductive system and breast disorders</p> <p>Testicular disorder</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>0 / 17 (0.00%)</p> <p>0</p> | <p>1 / 7 (14.29%)</p> <p>1</p> | |
| <p>Testicular infarction</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>0 / 17 (0.00%)</p> <p>0</p> | <p>1 / 7 (14.29%)</p> <p>1</p> | |
| <p>Respiratory, thoracic and mediastinal disorders</p> <p>Nasal congestion</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>2 / 17 (11.76%)</p> <p>2</p> | <p>0 / 7 (0.00%)</p> <p>0</p> | |
| <p>Adenoidal hypertrophy</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>0 / 17 (0.00%)</p> <p>0</p> | <p>1 / 7 (14.29%)</p> <p>1</p> | |
| <p>Atelectasis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>0 / 17 (0.00%)</p> <p>0</p> | <p>1 / 7 (14.29%)</p> <p>1</p> | |
| <p>Cough</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>2 / 17 (11.76%)</p> <p>3</p> | <p>1 / 7 (14.29%)</p> <p>1</p> | |
| <p>Epiglottic oedema</p> | | | |

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

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

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

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

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

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

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

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

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

| | | | |
|--|-----------------|----------------|--|
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Weight decreased | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| White blood cell count increased | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Prothrombin time prolonged | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 0 / 7 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Craniocerebral injury | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Facial bones fracture | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Fall | | | |
| subjects affected / exposed | 4 / 17 (23.53%) | 2 / 7 (28.57%) | |
| occurrences (all) | 5 | 3 | |
| Head injury | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Humerus fracture | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Infusion related reaction | | | |

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

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|---|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 7 (14.29%) 1 | |
| Talipes subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 7 (14.29%) 1 | |
| Portal venous system anomaly subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 7 (0.00%) 0 | |
| Cardiac disorders | | | |
| Tricuspid valve incompetence subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 7 (14.29%) 1 | |
| Tachycardia subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 1 / 7 (14.29%) 1 | |
| Sinus tachycardia subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 1 / 7 (14.29%) 1 | |
| Sinus bradycardia subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 7 (0.00%) 0 | |
| Right ventricular dysfunction subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 7 (14.29%) 1 | |
| Pulmonary valve incompetence subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 7 (14.29%) 1 | |
| Myocarditis subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 7 (0.00%) 0 | |
| Mitral valve incompetence subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 7 (14.29%) 1 | |
| Left ventricular hypertrophy subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 2 / 7 (28.57%) 2 | |

| | | | |
|---|-----------------------|---------------------|--|
| Coronary sinus dilatation subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 7 (14.29%) 1 | |
| Bundle branch block right subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 7 (14.29%) 1 | |
| Bradycardia subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 7 (14.29%) 1 | |
| Nervous system disorders Tremor subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 7 (0.00%) 0 | |
| Language disorder subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 7 (0.00%) 0 | |
| Seizure subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 1 / 7 (14.29%) 2 | |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 4 | 0 / 7 (0.00%) 0 | |
| Thrombocytosis subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 7 (0.00%) 0 | |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 9 / 17 (52.94%) 11 | 2 / 7 (28.57%) 2 | |
| Splenomegaly subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 7 (14.29%) 1 | |
| Neutrophilia subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 7 (14.29%) 1 | |
| Coagulopathy | | | |

| | | | |
|-----------------------------|----------------|----------------|--|
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Lymphopenia | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 7 (14.29%) | |
| occurrences (all) | 1 | 2 | |
| Leukopenia | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Leukocytosis | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 7 (14.29%) | |
| occurrences (all) | 1 | 1 | |
| Iron deficiency anaemia | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Immune thrombocytopenia | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Neutropenia | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Ear and labyrinth disorders | | | |
| Ear discomfort | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hypoacusis | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 7 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Otorrhoea | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Eye disorders | | | |
| Astigmatism | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Dry eye | | | |

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

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

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

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

| | | | |
|--|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 7 (14.29%) 1 | |
| Infections and infestations | | | |
| Adenovirus infection | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Atypical pneumonia | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Bacterial tracheitis | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 2 / 7 (28.57%) | |
| occurrences (all) | 6 | 2 | |
| Onychomycosis | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 1 / 7 (14.29%) | |
| occurrences (all) | 4 | 2 | |
| Metapneumovirus infection | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 0 / 7 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Influenza | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hand-foot-and-mouth disease | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Gastrointestinal viral infection | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Gastrointestinal bacterial overgrowth | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |

| | | | |
|--|----------------------|---------------------|--|
| Gastrointestinal bacterial infection subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 7 (0.00%) 0 | |
| Gastroenteritis viral subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 7 (0.00%) 0 | |
| Enterobiasis subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 7 (14.29%) 1 | |
| Ear infection staphylococcal subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 7 (14.29%) 1 | |
| Ear infection subjects affected / exposed occurrences (all) | 2 / 17 (11.76%) 2 | 0 / 7 (0.00%) 0 | |
| Cystitis subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 7 (0.00%) 0 | |
| Coxsackie viral infection subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 7 (14.29%) 1 | |
| Conjunctivitis subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 7 (0.00%) 0 | |
| Clostridium difficile infection subjects affected / exposed occurrences (all) | 2 / 17 (11.76%) 2 | 0 / 7 (0.00%) 0 | |
| Catheter site infection subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 7 (14.29%) 1 | |
| Candida infection subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 7 (14.29%) 1 | |
| COVID-19 subjects affected / exposed occurrences (all) | 4 / 17 (23.53%) 4 | 2 / 7 (28.57%) 2 | |

| | | |
|---|-----------------|----------------|
| Bronchitis | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 1 / 7 (14.29%) |
| occurrences (all) | 2 | 1 |
| Bronchiolitis | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 7 (14.29%) |
| occurrences (all) | 0 | 1 |
| Bacteriuria | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 |
| Tracheostomy infection | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 |
| Upper respiratory tract infection bacterial | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 |
| Skin candida | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 0 / 7 (0.00%) |
| occurrences (all) | 2 | 0 |
| Scarlet fever | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 0 / 7 (0.00%) |
| occurrences (all) | 2 | 0 |
| Rhinovirus infection | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 7 (14.29%) |
| occurrences (all) | 2 | 1 |
| Rhinitis | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 7 (0.00%) |
| occurrences (all) | 2 | 0 |
| Respiratory tract infection bacterial | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 |
| Respiratory tract infection | | |
| subjects affected / exposed | 3 / 17 (17.65%) | 0 / 7 (0.00%) |
| occurrences (all) | 3 | 0 |
| Respiratory syncytial virus infection | | |

| | | |
|--|-----------------|----------------|
| subjects affected / exposed | 3 / 17 (17.65%) | 0 / 7 (0.00%) |
| occurrences (all) | 4 | 0 |
| Respiratory syncytial virus bronchiolitis | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 |
| Rectal abscess | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 7 (14.29%) |
| occurrences (all) | 0 | 1 |
| Pseudomonas infection | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 7 (14.29%) |
| occurrences (all) | 0 | 1 |
| Pneumonia pneumococcal | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 7 (14.29%) |
| occurrences (all) | 0 | 1 |
| Pneumonia aspiration | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 7 (14.29%) |
| occurrences (all) | 0 | 1 |
| Pneumonia | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 7 (14.29%) |
| occurrences (all) | 1 | 2 |
| Pharyngitis | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 0 / 7 (0.00%) |
| occurrences (all) | 2 | 0 |
| Otitis media staphylococcal | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 7 (14.29%) |
| occurrences (all) | 0 | 1 |
| Otitis media acute | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 |
| Otitis media | | |
| subjects affected / exposed | 4 / 17 (23.53%) | 4 / 7 (57.14%) |
| occurrences (all) | 5 | 7 |
| Otitis externa | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 7 (14.29%) |
| occurrences (all) | 0 | 2 |

| | | | |
|---|-----------------|----------------|--|
| Oral candidiasis | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 7 / 17 (41.18%) | 3 / 7 (42.86%) | |
| occurrences (all) | 15 | 6 | |
| Tracheitis | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 7 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Urinary tract infection bacterial | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 5 / 17 (29.41%) | 4 / 7 (57.14%) | |
| occurrences (all) | 7 | 9 | |
| Metabolism and nutrition disorders | | | |
| Hypernatraemia | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 7 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Feeding intolerance | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Hypercholesterolaemia | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hypertriglyceridaemia | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 1 / 7 (14.29%) | |
| occurrences (all) | 2 | 2 | |
| Hypochloraemia | | | |

| | | | |
|-----------------------------|-----------------|----------------|--|
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 3 / 17 (17.65%) | 0 / 7 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 7 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Vitamin A deficiency | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Vitamin D deficiency | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 0 / 7 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Hyperuricaemia | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 2 / 7 (28.57%) | |
| occurrences (all) | 1 | 2 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|--------------|---|
| 14 June 2017 | <ul style="list-style-type: none">• 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 | <ul style="list-style-type: none">• Deleted Day 0.• Corrected typographical and grammatical errors, errors discovered during a QC check of the document (including references), inconsistencies in text between documents. |

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| 25 January 2018 | <ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> 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 | <ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> 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 | <ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> 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: <ul style="list-style-type: none"> 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. |

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| 01 May 2019 | <ul style="list-style-type: none"> • 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 | <ul style="list-style-type: none"> • 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 | <ul style="list-style-type: none"> • 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. |

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| 07 April 2020 | <ul style="list-style-type: none"> • 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. <p>Number of participants changed to reflect the number of subjects enrolled in Part 2.</p> <ul style="list-style-type: none"> • Administrative changes made for corrections, consistency, clarity and accuracy. <p>Included Pulmonary Adjudication Committee for completeness.</p> <ul style="list-style-type: none"> • Modifications made to align with IB. <p>Modifications in objectives wording to align with objectives in synopsis</p> <p>Text moved and modified to align with Sponsor protocol template and consistency across studies.</p> <ul style="list-style-type: none"> • 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 | <ul style="list-style-type: none"> • Added new section <ul style="list-style-type: none"> 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. |

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| 16 November 2020 | <ul style="list-style-type: none"> • 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. |
| 16 November 2020 | <ul style="list-style-type: none"> • 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. |

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| 15 January 2021 | <ul style="list-style-type: none"> • 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 | <ul style="list-style-type: none"> • 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 | <ul style="list-style-type: none"> • 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. |

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| 16 May 2023 | <ul style="list-style-type: none"> • Revised synopsis to update the endpoints based on the current enrollment, dosing and collected data. • Revised synopsis and its sections to: <ul style="list-style-type: none"> 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 | <ul style="list-style-type: none"> • 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. |

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| 17 May 2024 | <ul style="list-style-type: none">• 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). |
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported