STATISTICAL ANALYSIS PLAN

Version 4.0

15-APR-2024

ASPIRO: A Phase 1/2/3, Randomized, Open-Label, Ascending-Dose, Delayed-Treatment Concurrent Control Clinical Study to Evaluate the Safety and Efficacy of AT132, an AAV8-Delivered Gene Therapy in X-Linked Myotubular Myopathy (XLMTM) Participants

ASPIRO

ISN/Protocol ATX-MTM-002 (AT132-02)

IND 017367

EudraCT 2017-000876-27

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Version History

SAP Version History Summary

The changes from the prior approved SAP that impact analyses are listed with the rationale in the table below.

SAP Version	Approval Date	SAP Section(s)	Change	Rationale
1.0	09-Nov-2018		Not Applicable	Original Version
2.0	23-Jun-2019		Incorporating Part 1 and Part 2	Aligning SAP to protocol amendments.
3.0	10-Jan-2024	All	Formatted SAP to Astellas template, removed mention of Audentes, and streamlined text.	Consistency with Astellas standard document formatting.
3.0	10-Jan-2024	Objectives (1.1.1), Study Design (1.2)	Updated objectives and study design to align with Protocol version 11.0	The study goals changed from a hypothesis testing framework to a descriptive study framework.
3.0	10-Jan-2024	Endpoints (1.1.2)	- Moved the key secondary endpoint(s) "motor milestones achieved, change from baseline in CHOP INTEND, and change from baseline in PedsQL" to secondary endpoints. Replaced key secondary endpoint with "Percentage of subjects achieving functionally independent sitting for at least 30 seconds by Week 24" - Removed EQ-5D-Y and EQ-5D-5L secondary endpoints. - Removed "Change from baseline in the mRNA transgene ratio in the muscle biopsy" and "change from baseline in the quantitative analysis of muscle biopsies" from exploratory endpoints.	Aligning SAP to protocol Amendment version 11.0
3.0	10-Jan-2024	Estimand (1.1.3)	Added description of estimand	Aligning SAP to protocol Amendment version 11.0
3.0	10-Jan-2024	Study Design	Streamlined wording of study design for clarity. Removed reference to Schedule of Events. All data relating to control treatment period and INCEPTUS will not be used in the analysis. Added description of plan regarding primary analysis/database lock and final analysis/database lock to align with reporting requirements.	Aligning SAP to protocol Amendment version 11.0. Determination made that a primary CSR is necessary, so description of database lock plan is added.
3.0	10-Jan-2024	Randomization (1.3) and Analysis Sets (3)	Data will be analyzed as treated rather than 'as randomized'. Additional clarity added andthe analysis sets are updated to align with new goals of the study and protocol version 11.0	Aligning SAP to protocol Amendment version 11.0

SAP Version	Approval Date	SAP Section(s)	Change	Rationale
3.0	10-Jan-2024	Analysis Sets (3)	Changed mITT to FAS, as well as updated the definition to align with Protocol V.11.0 to require at least one dose of AT132 administered to fall into the analysis set. Additionally, removed ITT and PPS analysis sets.	Aligning SAP to protocol Amendment version 11.0
3.0	10-Jan-2024	General Considerations (4.1)	Aligned summary presentation to Protocol V11.0 study design. Removed details which per the new SAP template belong in the TLF Specifications. Descriptions of groupings moved to the "Analysis Sets" section. Statement added regarding how all data presentation will be descriptive. Definitions and derived variables are defined within the relevant sections.	Aligning SAP to protocol Amendment version 11.0
3.0	10-Jan-2024	Endpoints (1.1.2), Definition of Secondary Endpoints (4.4.2.1), Main Analytical Approach (4.4.2.2.7)	Changed the wording of a secondary endpoint from "Percentage of participants achieving full ventilator independence in the absence of acute illness and perioperatively at Week 24" to "Percentage of participants achieving full ventilator independence at Week 24". This is a change from the protocol.	During SAP creation process it was determined that the stipulations added to the endpoint were not relevant or meaningful.
3.0	10-Jan-2024	Endpoints (1.1.2),, Exploratory Endpoints (4.5.1.1), Main Analytical Approach (4.5.1.2)	Removed the following endpoint from exploratory analysis "In-depth interviews to assess the experiences and perspectives of caregivers and children with XLMTM." This is a change from the protocol.	Data for this endpoint was not available for analysis.
3.0	10-Jan-2024	Study Participants (4.2)	Added clarification and additional details to align with Protocol Version 11.0. Analysis sets provided in disposition summary updated to align with Protocol V11.0. Time-points of interest updated to align with Protocol V11.0. Presentation of protocol deviations limited to only the major ones that fall into pre-defined categories of interest, rather than presenting all protocol deviations, per SAP template.	Aligning SAP to protocol Amendment version 11.0
3.0	10-Jan-2024	Demographic and Other Baseline Characteristics (4.2.4)	Demographic summaries updated to include one for randomized participants for CT.gov reporting purposes. In addition, baseline characteristics updated to include only the relevant ones with corresponding data able to be summarized. Removed bar chart of medical history.	Aligning SAP to protocol Amendment version 11.0; CT.gov reporting requirements. Bar chart removed due to being externaneous.

SAP Version	Approval Date	SAP Section(s)	Change	Rationale
3.0	10-Jan-2024	Glucocorticoid Administration (4.2.6)	Summary updated to remove summary statistics of total dose administered. Details added regarding presentation of data related to taper.	Analysis aligned to what data is considered relevant.
3.0	10-Jan-2024	Extent of Exposure (4.2.7)	Summary of duration on study added.	Requested by clinical team.
3.0	10-Jan-2024	Primary Endpoint Analysis (4.3), Secondary Endpoint Analysis (4.4), Exploratory Endpoint Analysis (4.5)	Definition of baseline updated for primary analysis. Hypothesis testing removed. All analyses updated to align with Protocol Version 11.0 endpoints. Sensitivity analysis updated. Clarification added for motor milestones missing data imputation logic for protocol V1.0 - 4.0.	Aligning SAP to protocol Amendment version 11.0
3.0	10-Jan-2024	Main Analytical Approach	Choice of covariance structures if the unstructured structure doesn't converge has been updated. All comparisons and hypothesis testing has been removed from the primary analysis. MMRM results will only be presented for the change from baseline Week 24 time-point. Analysis dataset for analysis has been updated to FAS. Removal of continuous baseline values (e.g., age, ventilator status and duration, as well as baseline values for CHOP-INTEND, MIP and MFM20/32) being used as covariates in the MMRM.	Aligning SAP to protocol Amendment version 11.0; simplifying the model structure.
3.0	10-Jan-2024	Definition of Key Secondary Endpoint (4.4.1.1)	Removed logic for deriving missing motor developmental milestones. Due to the changes of objective of V 11.0 of the protocol, simple descriptive statistics of only available results were considered sufficient for the purpose.	Simplifying the analysis given the descriptive nature of the study.
3.0	10-Jan-2024	Main Analytical Approach of Secondary Endpoints (4.4.2.2)	Additional details added regarding analysis. Aligned to protocol V 11.0. Removed comparisons between groups. Removed correlation analysis. Updated scoring algorithms to align with scoring instructions. Removed logic for deriving missing motor developmental milestones and wording around adjudication of motor milestones.	Aligning SAP to protocol Amendment version 11.0; adding details for clarity of definitions
3.0	10-Jan-2024	Main Analytical Approach of Exploratory Endpoints (4.5.1.2)	Additional details added regarding analysis. Aligned to protocol V 11.0. Removed comparisons between groups. Removed correlation analysis. Updated scoring algorithms to align with scoring instructions. Removed analysis of subscores for questionnaires.	Aligning SAP to protocol Amendment version 11.0; adding details for clarity of definitions

SAP Version	Approval Date	SAP Section(s)	Change	Rationale
3.0	10-Jan-2024	Safety Analysis (4.6)	Removed Interferon-gamma and developmental parameters endpoints.Added hospitalization rate and annualized respiratory and non-respiratory SAE rate, and length of stay per hospitalization as endpoints.	Aligning SAP to protocol Amendment version 11.0
3.0	10-Jan-2024	Adverse events (4.6.1)	Added definitions of periods as well as analysis by period. AESI definitions have been updated. Additional AE summaries have been added. Additional details added on the AE analysis. Addition of swimmer plots and COVID-19 analysis.	Definitions aligned to the invstigator brochure as well as more clearly described. Modifications made for more interpretable analysis.
3.0	10-Jan-2024	Additional Safety Assessments (4.6.2)	Additional detail and clarifications added to align with Protocol Version 11.0. Liver safety assessments section added. Developmental parameters section removed. Added liver safety analysis. Vital sign and ECG threshold criteria and analyses updated.	Aligning SAP to protocol Amendment version 11.0. Modifications made for more interpretable analysis.
3.0	10-Jan-2024	Biodistribution and Viral Vector Shedding (4.7.1.2)	Updated analyses to correspond to what is considered meaningful.	Aligning SAP to data needed for the label.
3.0	10-Jan-2024	Subgroup Analysis (4.7.2)	Subgroup analyses have been removed	Aligning SAP to protocol Amendment version 11.0
3.0	10-Jan-2024	Baseline Definition (4.10.1)	Baseline definition updated to exclude information from INCEPTUS study.	Aligning SAP to protocol Amendment version 11.0
3.0	10-Jan-2024	Analysis Windows	Analysis windows have been updated to accommodate the longer follow-up to align to Protocol V 11.0. Additional details on windowing daily diary data have been added	Aligning SAP to protocol Amendment version 11.0; adding details for clarity of definitions
4.0	15-Apr-2024	Protocol Deviations (4.2.2)	Category definition for the protocol deviations has been updated.	Aligning SAP to Protocol Deviation Plan
4.0	15-Apr-2024	Percentage of participants achieving full ventilator independence at Week 24 (4.4.2.2.7)	The following statement has been removed: "Note: this endpoint definition is different from what is specified in the protocol at the time of SAP development (V11.0). It was updated from "Percentage of participants achieving full ventilator independence in the absence of acute illness and perioperatively at Week 24" to "Percentage of participants achieving full ventilator independence at Week 24" in the SAP".	Aligning SAP to protocol Amendment version 12.0

SAP Version	Approval Date	SAP Section(s)	Change	Rationale
4.0	15-Apr-2024	Table 6. Potentially Clinically Significant Criteria for Vital Signs (4.6.2.3) Table 7. Potentially Clinically Significant Criteria for ECG (4.6.2.4)	For Age Group, "> 7 years" has updated to "≥ 8 years".	For clarification purpose.
4.0	15-Apr-2024	Hospitalization (4.6.2.5.3)	Category definition for the annualized hospitalization rate has been updated.	Correcting a typographical error
4.0	15-Apr-2024	Analysis Windows (4.10.2)	Analysis windows have been updated according to schedule of assessment in Protocol V 11.0. Additional details have been added for analysis week windows for weekly average hours of ventilator support from diary of ventilator dependence.	Aligning SAP to schedule of assessments in protocol; analysis visit windows should have varied across endpoints based on protocol-defined visit schedule
4.0	15-Apr-2024	Appendix 2 Unfavorable Values for Efficacy Estimand Imputation (5.2)	An item of "Reduction in require ventilator support to ≤ 16 hours/day" has been removed.	Not needed to apply the imputation rule for this variable
4.0	15-Apr-2024	Appendix 2 Unfavorable Values for Efficacy Estimand Imputation (5.2)	For the 3rd column header "Imputed value after ICE occurrence through Week 24", "Week 24" has been updated to "Week 48".	For clarification purpose.

1 INTRODUCTION

This Statistical Analysis Plan (SAP) contains technical and detailed elaboration of the principal features of the analysis described in the protocol, and includes procedures for executing the statistical analysis to fulfil the objectives of the study.

The final SAP will be approved prior to database lock.

If there are any changes from the planned analyses in the final version of the SAP that impact the statistical analyses, then it will be documented in the Clinical Study Report (CSR).

1.1 Objectives, Endpoints and Estimands

1.1.1 Objectives

The objectives of the study are as follows:

- To determine the therapeutic dose of AT132
- To confirm the safety and efficacy of the therapeutic dose of AT132

1.1.2 Endpoints

Safety Endpoints:

- Adverse events (AEs), serious AEs (SAEs), and findings from safety laboratory tests, 12-lead electrocardiogram (ECG), echocardiograms (ECHOs), vital signs, growth parameters, physical examinations, liver ultrasounds, antibody formation (anti AAV8, anti MTM1), viral shedding, annualized hospitalization rate, annualized respiratory and non-respiratory SAE rate, and length of stay per hospitalization

Primary Efficacy Endpoint:

- Change from baseline in hours of ventilation support at Week 24

Key Secondary Efficacy Endpoint:

- Percentage of participants achieving functionally independent sitting for at least 30 seconds by Week 24

Other Secondary Efficacy Endpoints:

- Time to reduction in required ventilator support to ≤ 16 hours a day (only in participants who require invasive ventilation) at Week 24
- Change from baseline in Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) at Week 24
- Change from baseline in maximal inspiratory pressure (MIP) at Week 24
- Change from baseline in quantitative analysis of myotubularin expression in the muscle biopsy at Week 24
- Change from baseline in quality of life assessments at Week 24 (ie, the Assessment of Caregiver Experience with Neuromuscular Disease [ACEND] and Pediatric Quality of Life Inventory [PedsQL])

- Number (%) of age-appropriate clinically relevant gross motor function milestones attained through Week 24
- Percentage of participants achieving full ventilator independence at Week 24
- Survival

Exploratory Endpoints:

- Time to unassisted sitting for 30 seconds or more at Week 24
- Change from baseline in the Motor Function Measure scale (MFM-32) at Week 24
- Change from baseline in total raw score in the gross motor domain of the Bayley Scales of Infant and Toddler Development III (Bayley-III) at Week 24
- Change from baseline in total raw score in the fine motor domain of the Bayley-III at Week 24
- Change from baseline in the proportion of participants being able to feed without a gastrostomy or G tube at Week 24
- Change from baseline in the Communicative Development Inventories (CDI) scores at Week 24
- Change from baseline in the Parental Global Impression of Secretion Severity (PGIS-S) score at Week 24
- Change in the Parental Global Impression of Secretion Improvement (PGIS-I) score at Week 24
- Change from baseline in Clinical Global Impression of Severity (CGI-S) at Week 24
- Change in the Clinical Global Impression of Improvement (CGI-I) score at Week 24

1.1.3 Estimand

The estimand of the primary objective is defined by the following 5 attributes:

- Treatment: Single dose of AT132
- Population: Male participants with ventilator-dependent XLMTM, as defined by the inclusion/exclusion criteria of the study
- Endpoint: Change from baseline in hours per day of ventilation support at Week 24
- Intercurrent events and their corresponding strategies: For study discontinuation due to death or due to lack of efficacy, a composite strategy will be adopted, where participants with the intercurrent event before Week 24 having missing observation(s) after the intercurrent event will have those missing observations(s) imputed by unfavorable values (Appendix 2)
- Population level summary: Mean change from baseline, by AT132 dose level

The estimand framework described above will be applied to all relevant primary and secondary efficacy endpoints.

1.2 Study Design

This is a Phase 1/2/3, randomized, open-label, ascending-dose, delayed-treatment concurrent control clinical study to evaluate the safety and efficacy of AAV8-delivered gene therapy in XLMTM participants aged less than 5 years old. Participants will receive a single dose of AT132 and be followed for safety and efficacy for 10 years.

The study consists of 2 parts. Part 1 would establish the optimal dose of AT132. Part 2 would confirm the safety and efficacy of AT132 at the optimal dose level. The following describes how each part was designed and the changes as of protocol v8.

Part 1 (fully dosed as of protocol v8):

A maximum of 3 dose levels of AT132 are planned for evaluation in Part 1 of this study (Figure 1). Four participants will be enrolled in each dose level cohort, including 1 participant in each dose level cohort randomized to control with delayed administration of treatment. The first participant in each dose level cohort will be assigned to receive AT132 and will be treated as a sentinel participant. Subsequent participants in that dose level cohort will be randomized (2:1) to treatment or control with delayed treatment if there are no safety concerns after at least 4 weeks of post-dose data from the sentinel participant is evaluated by the chair of the data monitoring committee (DMC). Dose escalation to the next dose level will be considered after evaluation of at least 4 weeks of data from all participants dosed at the current dose level. Following the dose escalation portion of the study, an optimal dose will be determined in conjunction with the DMC, and control participants will be treated at the optimal dose level.

This study's independent DMC will monitor participant safety and provide recommendations to the Sponsor regarding dose level determination, cohort expansion, and safety and study conduct matters.

Control participants will generally have the same assessments as treated participants but on a less frequent schedule to lessen the burden of study participation. It is anticipated that control participants will participate for at least 24 weeks before an optimal dose is determined and the participant can be administered AT132. Following determination of the optimal dose, control participants will undergo pretreatment baseline procedures to confirm that they remain eligible to receive treatment with AT132 at the optimal dose. Once eligible, control participants will be dosed with AT132, and will initiate the post dose procedures.

Treated participants will be administered a course of concomitant prophylactic glucocorticoid (oral prednisolone) therapy commencing 1 day prior to AT132 dosing, and continuing for a period of approximately 8 weeks, then tapering from the original dose over an additional 8 weeks, per Investigator discretion, as a preventative measure for immune-mediated hepatic injury, which has been observed in gene therapy clinical studies with AAV. Tapering duration may be altered and/or supplemental administration of IV steroids (e.g., methylprednisolone) or other immunosuppressive regimens may be considered in cases of potential malabsorption of oral medications.

Participants will be followed for a total of 10 years following AT132 administration. See Figure 1 for the individual study participation timeline (Parts 1 & 2) through Week 48.

Part 2 (described herein as planned prior to protocol v8; partially dosed as of protocol v8):

In Part 2, the optimal dose of AT132 will be evaluated in an expansion cohort of 10 participants age matched randomized to a study drug or a delayed-treatment control group

(1:1 allocation ratio). A pair of participants in each group will be prospectively best-matched based on age (±6 months) before being randomized to 1 of the treatment arms (AT132 vs. delayed-treatment control). The administration of study drug and concomitant prophylactic glucocorticoids, and the assessment of safety will be the same as described in Part 1. Following collection of their Week 24 data, control participants will be administered AT132 and followed according to the Schedule of Events.

Part 2 as of protocol v8 and v9:

Following the review of benefit/risk profiles of the 1.0×10^{14} vg/kg and 3.0×10^{14} vg/kg dose levels, the Sponsor, in consultation with the DMC, determined that participants not yet dosed were to be administered the lower dose level (ie, the therapeutic dose), which is 1.3×10^{14} vg/kg as determined by the 2nd generation vg titer assay. Dosing of the 3 enrolled delayed-treatment controls who have not yet been dosed will not be conducted as described above for Part 2, but will resume at 1.3×10^{14} vg/kg as long as each participant meets a subset of inclusion and exclusion criteria prior to dosing. If any of these control participants is not eligible to be dosed, another eligible participant can be enrolled. Any new participant will not be considered a delayed-treatment control and therefore will not be required to wait 24 weeks before administration of study drug. Any new participant will be enrolled under all of the inclusion/exclusion criteria (including Exclusion Criteria 12-14 required for Part 2 participants).

In addition to prophylactic glucocorticoids, participants will receive daily prophylactic ursodiol (ursodeoxycholic acid) beginning between Study Days -6 and -4. Participants will be followed according to the Schedule of Events.

As of protocol v10 and beyond:

This study does not allow for enrollment or dosing of any future participants.

See Figure 2 for Overall Study Design.

Details of the schedule of clinical assessments are available in the protocol.

Figure 1 Summary of Individual Study Participation Timeline (Parts 1 & 2)

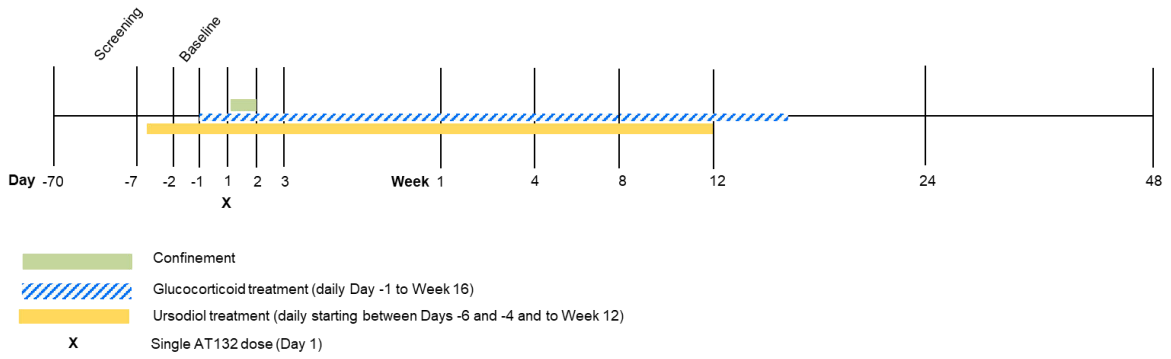
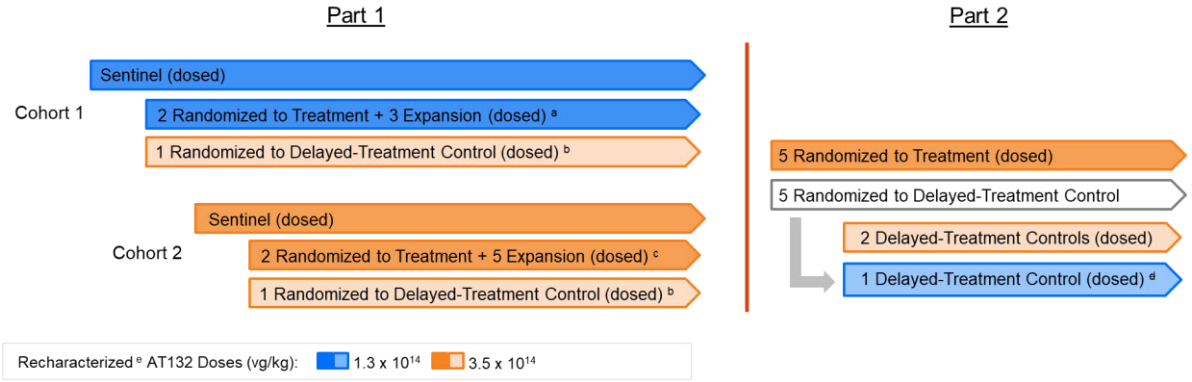


Figure 2 Overall Study Design



Notes: Delayed-treatment control subjects to be treated with AT132 after Week 24. As reflected in protocol v5, the Data Monitoring Committee (DMC) and Sponsor determined the therapeutic dose to be 3.0×10^{14} vg/kg and thus, dose escalation to the third originally planned 5.0×10^{14} vg/kg dose level (Cohort 3) did not occur.

a. An additional 3 subjects treated with 1.0×10^{14} vg/kg AT132 in Cohort 1 based on DMC recommendation.
b. Delayed-treatment control subjects from Part 1 treated with AT132 after the therapeutic dose was determined.
c. Additional subjects treated with 3.0×10^{14} vg/kg AT132 in Cohort 2 based on DMC recommendation.
d. No additional subjects will be dosed under this amendment.
e. Previously referred to as 1.0 and 3.0×10^{14} vg/kg. The 1.0×10^{14} vg/kg and 3.0×10^{14} vg/kg dose levels based on the 1st generation titer method equate to 1.3×10^{14} vg/kg and 3.0×10^{14} vg/kg, respectively, based on an analysis of all historical Study 002 drug product lots using the 2nd generation vg titer assay.

Source: Data on file.

Two database locks are planned for this clinical study. The first database lock is intended for will occur after all ongoing participants complete the Week 24 visit and prior to all participants completing the 10-year follow-up period or withdrawing. The second (final) database lock will occur after all participants have completed the study.

1.3 Randomization

Part 1: The first participant in each dose level cohort will be assigned to receive AT132 and will be treated as a sentinel participant. Subsequent participants in that dose level cohort will be randomized (2:1) to treatment or control with delayed treatment if there are no safety concerns after at least 4 weeks of post-dose data from the sentinel participant is evaluated by the chair of the DMC.

Part 2: (prior to protocol v8): Participants will be prospectively paired based on age (±6 months) before being randomized to study drug or delayed-treatment control (1:1 allocation) to one of the treatment arms (AT132 vs. delayed-treatment control).

General: Randomization codes will be preassigned for each participant before enrollment into the cohort.

After confirmation of participant's eligibility by the Investigator, the Sponsor will provide to the Investigator the assigned dose or control designation for the participant number according to the randomization sequence and the order of participants eligible for randomization.

ASPIRO Part 2 participants that are ready to be randomized will fall into one of the following groups:

- If 2 age-matched participants are ready and eligible for randomization, then they will be randomized (with a separate request form for each participant)

- If only 1 participant is ready for randomization, then
    - Two more check-list-qualified age-matched participants will be identified and confirmed by study sponsor (using protocol check list) before any attempt for randomization
    - The request for randomization of the first participant will include the participant ID numbers for the additional 2 participants identified as confirmed potentials
    - Amongst the 2 participants competing for randomization into the second slot for the pair, the following hierarchy will be used to prevent any bias in selecting the second participant
        - Site readiness
        - Date enrollment/eligibility authorization received
        - Closest in age to the first participant already randomized in that pair group
        - Duration of participation in INCEPTUS
        - Tie-breaker #1: Regional Diversity (i.e., site with no participants has priority)
        - Tie-breaker #2: Country Diversity (i.e., country with no participant has priority)
        - The form for request for randomization of the second participant will need to have a complete list of the above bullets for prioritization in form of a table

Once 2 participants have been randomized into the same age-matched pair is complete.

This is an open-label study, and therefore there is no blinding of treatment assignment for the study.

The objectives of the study changed as a result of the study going on clinical hold. The intent changed to describe the safety and efficacy of participants being administered a low dose or a high dose of AT132. As such, data is not analyzed as randomized, but instead, data analysis is based on low dose or high dose received and excludes the two non-dosed delayed control participants.

2 STATISTICAL HYPOTHESES

Considering that the study is no longer able to address the stated objectives, there will be no statistical hypothesis testing. All summaries by treatment group will be descriptive in nature..

3 ANALYSIS SETS

In accordance with International Conference on Harmonization (ICH) recommendations in guidelines E3 and E9, the following analysis sets will be used for the analyses.

The determination of whether participants are included or excluded from the safety and efficacy analysis sets will be made prior to database lock.

The following analysis sets for participants treated with AT132 will be used:

- Full Analysis Set (FAS) is defined as all randomized and/or enrolled participants who received AT132 and had at least 1 postdose efficacy assessment. The participants will be analyzed based on the treatment actually received. The FAS will be used for summary of demographics and baseline characteristics, and analyses of all efficacy endpoints.
- Safety Analysis Set (SAF) is defined as all randomized and/or enrolled participants who received AT132. The participants will also be analyzed based on the actual treatment received as well as an "All dosed" group of all participants treated with AT132. The SAF will be used for summaries of demographics, baseline characteristics, participant disposition, and the analysis of the safety endpoints.

In each analysis set, 3 treatment groups are defined by: (i) Low Dose (AT132 1.3×10^{14} vg/kg), (ii) High Dose (AT132 3.5×10^{14} vg/kg), and (iii) AT132 Dosed Total (not applicable to efficacy endpoints).

Listings will include all randomized participants unless otherwise stated.

4 STATISTICAL ANALYSES

4.1 General Considerations

The study is no longer able to address the stated objectives, hence the statistical analysis will provide descriptive summaries by treatment groups.

Continuous data will be summarized descriptively including the number of participants (n), mean, standard deviation (SD), median, minimum and maximum. Categorical data will be summarized by frequencies and percentages. Percentages by categories will be based on the number of participants with no missing data, i.e. the percentages for the non-missing categories will add up to 100%.

All data summarization and analyses will be performed using SAS® Version 9.4 or higher on Red Hat Enterprise Linux. Specifications for table, figures, and data listing formats can be found in the TLF specifications.

4.2 Study Participants

Participant disposition will be summarized for all randomized participants. Demographics and baseline characteristics will be summarized for both the FAS and SAF populations.

4.2.1 Participant Disposition

Disposition of participants will be summarized by AT132 dose level and overall. Denominator for percentages is the number of participants treated, unless otherwise specified.

The participant disposition summary will include:

- Number of participants with signed informed consent
- Number and percent of participants who were randomized (denominator is the number of participants with informed consent)
- Number and percent of participants who were treated (denominator is the number of participants randomized)
- Number and percent of participants who were not treated (denominator is the number of participants randomized)
- Number and percent of participants who complete 24 weeks of follow-up after initial dosing visit
- Number and percent of participants who complete 48 weeks of follow-up after initial dosing visit
- Number and percent of participants who complete 5 years of follow-up after initial dosing visit
- Number and percent of participants who complete 10 years of follow-up after initial dosing visit.
- Number and percent of participants who complete the study
- Number and percent of participants in each analysis set (FAS and SAF)
- Number and percent of participants who prematurely discontinue from the study
- For discontinuation, the primary reason reported by the investigator will be summarized using count and percent of participants.

4.2.2 Protocol Deviations

The number and percentage of participants with the following protocol deviation criteria will be summarized for each criterion and overall, by AT132 dose level and overall as well as by investigative site for all participants who were randomized. Participants deviating from a criterion more than once will be counted once for the corresponding criterion.

The unique identifiers will be as follows, and only apply to major deviations:

- PD1 - Inclusion/ Exclusion,
- PD2 - Withdrawal Criteria,
- PD3 - Study Intervention,
- PD4 - Excluded Concomitant Medications,
- PD5 - Informed Consent,
- PD6 - Safety Reporting,
- PD7 - Procedures/ Tests,
- PD8 - IRB/ Ethics Committee.

4.2.3 COVID-19 Impact

Assessments that were indicated in the eCRF as impacted by the COVID-19 pandemic will be listed.

4.2.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized descriptively by AT132 dose level and overall for all randomized participants (demographics only), the FAS, and SAF analysis set.

Demographic characteristics will include age at dosing (months), age group (< 1 year, 1 – <2 years, ≥ 2 years at the time of dosing), sex (all male), race, ethnicity, and country where participant resides.

The following baseline characteristics will be summarized:

- Growth Parameters:
    - Baseline weight
    - Height
    - Body mass index (BMI)
    - Head circumference
- Disease History:
    - Age at diagnosis of XLMTM
    - Age when first symptoms noted
- Ventilator History:
    - Ventilator type at baseline (invasive vs non-invasive)
    - Hours of ventilation support at baseline (Primary endpoint)
- Genetics and Baseline Protein Expression:
    - Category of genetic diagnosis (Nucleotide or base change, amino acid or codon change, Exon)
    - Myotubularin expression at baseline
- Endpoints at Baseline:
    - Motor Development Milestone assessments at baseline
    - Liver ultrasound at baseline result
    - CHOP-INTEND total score at baseline
    - MIP at baseline
    - Ability to sit unassisted ≥ 30 seconds

- Number of gross motor function milesones achieved at baseline

Medical history is coded in MedDRA, and will be summarized by System Organ Class (SOC) and Preferred Term (PT), by treatment group and overall for the SAF.

Participants genetic testing results will be listed.

4.2.5 Previous and Concomitant Medications

Previous and concomitant medications will be summarized by therapeutic subgroup (ATC 2nd level), chemical subgroup (ATC 4th level) and preferred World Health Organization (WHO) name (active ingredients for combination drugs) by AT132 dose level and overall for the SAF.

Participants taking the same medication multiple times will be counted once per medication and investigational period. A medication which can be classified into several chemical and/or therapeutic subgroups is presented in all chemical and therapeutic subgroups.

Previous medications are defined as medications that participants started prior to administration of study drug. Concomitant medications are defined as any medications that participants took on or after the date of administration of study drug and through the end of follow-up.

Medications that started prior to and continued after adminstration of study drug will be counted in both previous and concomitant medications.

4.2.6 Glucocorticoid Administration

Concomitant glucocorticoid administration will be summarized by AT132 dose level and overall for the SAF. Glucocorticoids will be identified by ATCr_CD = “H02AB”.

The glucocorticoid administration summary will include a summary table of:

- Duration of Taper
- Total days on protocol-specified glucocorticoid dose regimen (For subjects weighing < 60 kg, the dose will be 1 mg/kg prednisolone orally daily and for subjects weighing ≥ 60 kg, the dose will be 60 mg prednisolone orally daily) prior to taper (day prior to taper start date – Day -1 date + 1),

The day of taper start for a participant is defined as the date of first glucocorticoid record in the concomitant medication dataset where (frequency)*(dose) is less than the (frequency)*(dose) value for the initial glucocorticoid record in the dataset.

A listing of all subjects’ glucocorticoid administration will be provided.

Individual subject line plots of ALT x ULN, AST x ULN, Total Bilirubin x ULN, Direct Bilirubin x ULN, CK x ULN, serum bile acid x ULN, and Troponin T x ULN will be created, with a dashed vertical line indicating where the taper began.

A swimmer plot may be created to visualize the glucocorticoid administration progression.

4.2.7 Extent of Exposure

Participants' duration on study will be summarized descriptively for the SAF both as a continuous variable and by counts and percentages for the following categories:

- < 3 months
- 3 – < 6 months
- 6 – < 12 months
- 1 – < 2 years
- 2 – < 5 years
- 5 – < 7 years
- 7 – < 10 years
- 10 + years

Duration on study is defined as:

$$\frac{(max(Date\ of\ last\ day\ of\ follow\ up, date\ of\ discontinuation) - date\ of\ dosing + 1)}{365.25}$$

The information on drug dosing and study duration will be presented in a listing.

4.3 Primary Endpoint Analysis

4.3.1 Definition of Endpoint(s)

The primary efficacy endpoint is change from baseline in hours of ventilation support at Week 24.

The hours of ventilation support will be based on diary data from participants for whom diary data was collected at baseline (those administered AT132 under protocol v5 and beyond, including all participants in Part 2), and by assessment of time off ventilator questionnaire for all other participants (those administered AT132 under protocol v4 and prior). Weekly scores will be 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 indicates that ventilator type = "None", then zero will be imputed for the number of hours on ventilator.

The days included for the average for the particular visit week are defined by avisit="Week "||strip(put(ceil(ady/7),best.)), where ADY = the analysis visit day of the diary entry.

If at least 5/7 days of the visit week are non-missing, then the remaining missing values will be ignored in the calculation of average ventilation hours needed. Otherwise, if <5 non-missing diary records are available for the visit week, then up to 4 missing values will be imputed by the worst score of the week (most hours on ventilator), so that at least 5 records are available for calculating the average for the week.

Baseline is defined as the average of the diary data values in the 7 days leading up to and including the day of administration of the study drug (i.e. Analysis Day – 6 through Day 1). The missing data approach described in the paragraph above will be used if <7 days of data are available at baseline. If only non-diary ventilator questionnaire data is available at baseline, the last record prior to administration of study drug will be used for the baseline value.

4.3.2 Main Analytical Approach

The change from baseline in hours of ventilation support at Week 24 will be analyzed using a MMRM with treatment (low dose or high dose), time (Weeks 1, 4, 12, 16, 24, 36, and 48), and treatment by time interaction as fixed effects, baseline value of hours of ventilation support as the covariate, and within-participant repeated measure structure in the model.

To account for repeated measures within participants, the following within-participant covariance structure will be implemented:

1. An unstructured (UN) covariance matrix will be attempted first.
2. A heterogeneous Toeplitz covariance matrix will be attempted if the UN covariance matrix fails to converge.
3. A heterogenous compound symmetry (CS) covariance matrix will be attempted if the heterogenous Toeplitz covariance matrix fails to converge.
4. A homogenous CS covariance matrix will be attempted if the heterogenous CS covariance matrix fails to converge.

If the UN covariance matrix converges, the Kenward-Roger approximateion will be used to estimate the denominator degree of freedom. Othewise, under a more parsimonious structure, a modified covariance estimator will be used (Gosho, Noma, and Maruo, 2021).

The estimated change from baseline in hours of ventilation support at Week 24 will be summarized by AT132 dose level based on this model, including the standard error (SE) and 95% confidence interval (CI).

Participants who discontinue from the study prior to Week 24 due to death or due to lack of efficacy and who have missing observations after the intercurrent event occurs, will have those missing observations imputed by unfavorable values (i.e. 24 hours) in the analysis.

The primary analysis will be conducted using the FAS.

The hours of ventilation support and change from baseline will also be summarized descriptively by visit and AT132 dose level group.

A subject line plot of the hours of ventilation support at each time-point will be created.

4.3.3 Sensitivity Analysis

In order to assess the robustness of the primary analysis model with respect to non-monotone missing data, the primary efficacy endpoint will be analyzed using a mixed model repeated measures (MMRM) with baseline, treatment (low dose or high dose), time (all available visit weeks through Week 48), and treatment by time interaction as fixed effects and participant as

random effect. The change from baseline in hours of ventilation support at Week 24 will be summarized by dose level based on this model, including the 95% confidence interval.

The same analysis set and data used for the primary analysis (including imputations) will be used for the sensitivity analysis.

4.4 Secondary Endpoints Analysis

4.4.1 Key Secondary Endpoint

4.4.1.1 Definition of Endpoint

Percentage of participants achieving functionally independent sitting for at least 30 seconds by Week 24.

The primary source of data is the motor milestone eCRF. However, if that data isn't available for the visit, then Bayley III item #26 will be used to determine whether the participant achieves (Yes) or doesn't achieve (No) the milestone.

If both the motor milestone or the Bayley result are not available, but the participant attended the visit, then their result will be included in the summary as "missing".

4.4.1.2 Main Analytical Approach

The analysis of the key secondary endpoint will be conducted using the FAS.

The number and percentage of participants achieving functionally independent sitting for at least 30 seconds by Week 24 will be summarized descriptively by low dose and high dose groups.

In addition, the number and percentage of participants achieving functionally independent sitting for at least 30 seconds will be summarized descriptively by visit and dose level group.

4.4.2 Supportive Secondary Endpoints

4.4.2.1 Definition of Endpoints

- Time to reduction in required ventilator support to ≤ 16 hours a day (only in participants who require invasive ventilation) at Week 24
- Change from baseline in Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) at Week 24
- Change from baseline in maximal inspiratory pressure (MIP) at Week 24
- Change from baseline in quantitative analysis of myotubularin expression in the muscle biopsy at Week 24
- Change from baseline in quality of life assessments at Week 24 (ie, the Assessment of Caregiver Experience with Neuromuscular Disease [ACEND] and Pediatric Quality of Life Inventory [PedsQL])
- Number (%) of age-appropriate clinically relevant gross motor function milestones attained through Week 24
- Percentage of participants achieving full ventilator independence at Week 24
- Survival

4.4.2.2 Main Analytical Approach

The secondary efficacy analyses will be conducted for the FAS.

4.4.2.2.1 Time to reduction in required ventilator support to ≤ 16 hours a day (only in participants who require invasive ventilation) at Week 24

This endpoint will be summarized for low dose and the high dose groups separately in the participants who require invasive ventilation. Kaplan-Meier plots along with median (95% CI) time from the study start date to event will be provided.

The number of hours of ventilator support at each collected time point for this analysis will be taken directly from the daily diary (Protocol V5.0 and later) or by assessment of time off ventilator questionnaire (prior to Protocol V5.0). The first instance of time reduction reported as ≤ 16 hours per day will be considered an event. Participants will be censored at either Week 24 or withdrawal from study, whichever occurs first.

4.4.2.2.2 Change from baseline in Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) at Week 24

The change from baseline will be analyzed using the MMRM in a similar method to that used for the primary analysis of the primary efficacy endpoint, described in Section 4.3.2. Estimated change from baseline in CHOP INTEND score at Week 24 will be summarized by dose level.

In addition, the CHOP INTEND score and corresponding change from baseline at each visit will be summarized descriptively by dose level group.

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) (Glanzman, 2010) and has been validated for XLMTM (Duong, 2021). 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 ability 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.

If a participant has 2 assessments with a total score of ≥56, the CHOP INTEND will not be required for future visits.

Subject line plots of the CHOP INTEND over time will be created.

4.4.2.2.3 Change from baseline in maximal inspiratory pressure (MIP) at Week 24

The change from baseline will be analyzed using the MMRM in a similar method to that used for the primary analysis of the primary efficacy endpoint, described in Section 4.3.2. Estimated change from baseline in MIP at Week 24 will be summarized by dose level.

In addition, the MIP and corresponding change from baseline at each visit will be summarized descriptively by dose level group.

If a subject has discontinued the use of the ventilator and has 2 assessments with the MIP at 80 cmH2O, testing for MIP, MEP, and P0.1 will not be required for future visits.

Subject line plots of the MIP over time by will be created.

4.4.2.2.4 Change from baseline in quantitative analysis of myotubularin expression in the muscle biopsy at Week 24

The change from baseline will be analyzed using the MMRM in a similar method to that used for the primary analysis of the primary efficacy endpoint, described in Section 4.3.2. Estimated change from baseline in myotubularin expression levels at Week 24 will be summarized descriptively by dose level.

In addition, the myotubularin expression levels and corresponding change from baseline at each visit will be summarized descriptively by dose level group.

Subject line plots of the muotubularin expression levels over time will be created.

These data will also be listed.

4.4.2.2.5 Change from baseline in quality of life assessments at Week 24 (ie, the Assessment of Caregiver Experience with Neuromuscular Disease [ACEND] and Pediatric Quality of Life Inventory [PedsQL])

The change from baseline will be analyzed using the MMRM in a similar method to that used for the primary analysis of the primary efficacy endpoint, described in Section 4.3.2. Estimaged change from baseline in the ACEND and PedsQL scores (described below) at Week 24 will be summarized descriptively by dose level.

In addition, the ACEND and PedsQL scores and corresponding change from baseline at each visit will be summarized descriptively by dose level group.

Subject line plots of the ACEND and PedsQL scores over time will be created.

ACEND

The ACEND was developed to measure impact on the lives of parents/legally authorized representatives (LARs)/caregivers caring for children with severe neuromuscular disorders (Matsumoto, 2011). Several domains of the ACEND (time, finance, and emotion) are relevant to assessing the caregiver burden of the parents of children with XLMTM.

ACEND contains 41 items which reflect 2 domains (physical impact and general caregiver impact). The physical impact domain includes 4 sub-domains: feeding/grooming/dressing (6 items), sitting/play (5 items), transfers (5 items) and mobility (7 items). The general caregiver impact domain includes 3 sub-domains: time (4 items), emotion (9 items), and finance (5 items). Score for each item is based on the 6- or 5-point ordinal scale, and scores for each domain and subdomain are scored on a scale of 0 - 100. Higher scores reflect

caregivers experiencing less intense care-giving impact. Sub-domain and total scores are thus meant to confer "impact health" in each caregiver respondent (Xu, 2020).

Raw scores for each subdomain are created by computing the algebraic mean of the items for those respondents who completed one item or more; setting missing for those items with no responses. Then, the arithmetic mean of the responded items is standardized to a 0 to 100 score using the following formula:

$$100 * \frac{arithmetic\ mean\ of\ the\ items\ in\ subdomain - 1}{maximum\ item\ score\ in\ the\ subdomain - 1}$$

Transformed scores should be 0 to 100 for each subdomain.

A total score can be calculated as the mean of the 7 subdomain scores. Domain scores will be calculated as the mean of the sub-domains. When any subdomain scores are missing, the total score (or domain score) will be missing. No items, subdomain scores, domain score, or total scores will be imputed.

Total scores and corresponding change from baseline will each be analyzed by MMRM as described above at Week 24 and summarized descriptively by dose level group and visit.

PedsQL

The 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. The 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.

The PedsQL neuromuscular module was designed to measure health-related quality of life dimensions specific to children aged 2-18 years with neuromuscular disorders and has been validated in other neuromuscular disorders such as SMA (Iannaccone, 2009). This is the module of the questionnaire that is used in this study, and is considered suitable to be used for children < 2 years of age.

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)
- Total Scale Score

Higher scales/scores indicate lower problems.

Scores are derived in the following way:

- Step 1: Transform Score

  - Items are reversed scored and linearly transformed to a 0-100 scale as follows: 0=100, 1=75, 2=50, 3=25, 4=0.

- Step 2: Calculate Scores by Dimensions x
  - If more than 50% of the items in the scale are missing, the scale scores should not be computed, x Mean score = Sum of the items over the number of items answered.
  - If more than 50% of the items in the scale are missing, the Scale Scores should not be computed.
  - If 50% or more items are completed: Impute the mean of the completed items in a scale.
- Total Score: Sum of all the items over the number of items answered on all the Scales.

Per protocol, the parent-report version of the questionnaire is supposed to be administered. In the case that the child-report version of the questionnaire is administered, the scoring algorithm will be adjusted accordingly.

Total scores and corresponding change from baseline will each be analyzed by MMRM at Week 24 as described above and summarized descriptively by dose level group and visit.

4.4.2.2.6 Number (%) of age-appropriate clinically relevant gross motor function milestones attained through Week 24

Protocol versions 1 to 4:

Bayley and motor milestone collection was intermittent and not required in versions 1 – 4 of the protocol, so data may be missing for some participants at some visits. In addition, the motor milestone eCRF was not added until version 5.0 of the protocol. As such, the Bayley III item (referenced in Table 1) corresponding to each motor milestone will be used for the analysis of the motor milestone data collected under protocol version 1 – 4. If the Bayley III result is not available for the visit, but the participant attended the visit, then their result will be included in the summary as "missing".

Protocol versions 5+:

The motor developmental milestones listed in Table 1 below will be derived in form of Yes (achieved) and No (not achieved).

Any motor milestone value that is collected prior to participants' date of signing the informed consent for Protocol Version 5.0 will use the flowchart logic described in the "Protocol versions 1 to 4" section above for deriving the motor milestone achievement status. Records collected after that date will follow the logic corresponding to the "Protocol versions 5+" section.

Table 1 Motor Developmental Milestones

Development Milestone	Reference	Summary Description of Performance Criteria*	Expected Age of Achievement for Analysis (months)
Head Control	Bayley-III Gross Motor Subtest Item #9	Child holds head erect for at least 15 seconds without support	4.0†
Rolls from Back to Sides	Bayley-III Gross Motor Subtest Item #20	Child turns from back to both right and left sides	6.0†
Sits Without Support	*WHO Multicentre Growth Reference Study*	Child sits alone without support for at least 10 seconds	9.2^‡
Sits Without Support	Bayley-III Gross Motor Subtest Item #26	Child sits alone without support for at least 30 seconds	9.2^‡
Stands with Assistance	Bayley-III Gross Motor Subtest Item #33	Child supports own weight for at least 2 seconds	11.4^
Crawls	Bayley-III Gross Motor Subtest Item #34	Child makes forward progress of at least 5 feet by crawling on hands and knees	13.5^
Pulls to stand	Bayley-III Gross Motor Subtest Item #35	Child raises self to standing position using chair or other convenient object for support	12.0†
Walks with Assistance	Bayley-III Gross Motor Subtest Item #37	Child walks by making coordinated, alternating stepping movements. He/she may hold on with 1 or 2 hands for support.	13.7^
Stands Alone	Bayley-III Gross Motor Subtest Item #40	Child stands alone for at least 3 seconds after you release his or her hands.	16.9^
Walks Alone	Bayley-III Gross Motor Subtest Item #42	Child takes at least 3 steps without support, even if gait is stiff-legged and wobbly	17.6^

* See motor milestone manual for full description of performance criteria
† Per CDC. For the milestones covered by the CDC, the age at which >75% of children attained the milestone is used as the reference for analysis here.
^ Per WHO Multicenter Growth Reference Study (MGRS), 2006. For the milestones covered by the WHO MGRS, the upper bound of the range (1-99%) is used as the reference for analysis here.
‡ Duration of sitting in the reference (WHO Multicenter Growth Reference Study) is not clearly defined, so the same age is used for the expected age of achievement for both independent sitting milestones.

The number and percentage of participants achieving each gross motor function milestone will be summarized descriptively by low dose and high dose group by visit week through Week 24. A similar summary will be provided for visits occurring after Week 24.

The denominator of the percentage calculation will only include the participants who attended the visit and are expected to achieve the particular milestone based on their age (i.e., if at the time of an assessment the child is at least the age indicated in Table 1, then they will be considered eligible for the milestone and will be included in the denominator). A child's eligibility will need to be uniquely determined for each assessment at each time-point.

The denominator values will be included in the table.

The percent of age-eligible milestones that each participant achieves at Week 24 will also be summarized as a continuous (percentage) by visit and via shift table as an ordinal variable, by number and percent of participants in each category (None, at least 1, >1 to half of the expected milestones, >50% to <100% all expected milestones, All expected milestones) at baseline and shift post-baseline.

Number of age-eligible milestones expected at Week 24 (denominator for the calculation for the participant at the visit) is determined based on the age of the participant at the visit and the corresponding number of milestones expected for that age. The numerator of the calculation for the participant at the visit is the number of milestones that they have achieved. The corresponding percentage will be converted to the relevant category. The number of participants falling into each category regardless of age will be summarized at each visit.

Each participant's timeline of achieving the motor milestones will also be presented graphically.

Any assessment done prior to the date of the participant signing Protocol V 5.0 informed consent is assumed to correspond to protocol V1.0 – 4.0 data.

4.4.2.2.7 Percentage of participants achieving full ventilator independence at Week 24

"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.

The number and percentage of participants achieving full ventilator independence at Week 24 will be summarized descriptively by low dose and high dose groups.

In addition, a summary by visit week of the same parameter will be provided by dose level.

All ventilator parameter data will be listed.

4.4.2.2.8 Survival

This endpoint will be summarized for low dose and the high dose groups separately for all participants in the FAS. Kaplan-Meier plots of time from the dosing date to event will be provided. In addition, the estimated survival rate at the following time-points will be presented by dose level group:

- 3 months
- 6 months
- 1 year
- 2 years
- 5 years
- 10 years

For this analysis, the date of a participant's death is considered the time of an event. Survival status should be assessed at each visit until the participant withdraws consent or completes the study. If the participant misses a visit or withdraws for a reason other than withdrawal of consent or death, the site should contact the parent(s)/LAR(s) to ascertain if the participant is

alive. For participants who withdraw from the study, the participant should be contacted every 6 months for 5 years after administration and every year for an additional 5 years (after the 5-year follow-up through 10-years follow-up) to assess for survival. If not alive, the cause and date of death should be requested and recorded.

Participants will be censored at the last known date/time of contact.

4.5 Exploratory Endpoints Analysis

The analysis of exploratory efficacy endpoints will be conducted using the FAS.

4.5.1.1 Definition of Endpoints

- Time to unassisted sitting for 30 seconds or more at Week 24
- Change from baseline in the Motor Function Measure-32 (MFM-32) at Week 24
- Change from baseline in total raw score in the gross motor domain of the Bayley Scales of Infant and Toddler Development III (Bayley-III) at Week 24
- Change from baseline in total raw score in the fine motor domain of the Bayley-III at Week 24
- Change from baseline in the proportion of participants being able to feed without a gastrostomy or G-tube at Week 24
- Change from baseline in the Communicative Development Inventories scores at Week 24
- Change from baseline in the Parental Global Impression of Secretion Severity (PGIS-S) score at Week 24
- Change in the Parental Global Impression of Secretion Improvement (PGIS-I) score at Week 24
- Change from baseline in Clinical Global Impression of Severity (CGI-S) at Week 24
- Change in the Clinical Global Impression of Improvement (CGI-I) score at Week 24

4.5.1.2 Main Analytical Approach

4.5.1.2.1 Time to unassisted sitting for 30 seconds or more at Week 24

This endpoint will be summarized for low dose and the high dose groups separately for all participants in the FAS. Kaplan-Meir plots along with median (95% CI) time from the study start date to event will be provided.

The event of successful unassisted sitting for 30 seconds is defined as described in Section 4.4.1.1. Participants who meet the described criteria will be considered to have an event. All other participants will be censored

4.5.1.2.2 Change from baseline in the Motor Function Measure-32 (MFM-32) at Week 24

MFM-20 and MFM-32 total and dimension scores will be summarized descriptively by visit and dose level group. For the MFM-20 by-visit summary, if participants were administered the MFM-32, then the MFM-20 questions/derivations will be used from those assessments to derive the MFM-20 result for summary purposes.

Regardless of whether the participants were administered MFM-32 or MFM-20, the observed total and dimension scores and corresponding change from baseline at each visit will be listed. The listing will include a column indicating which version of the questionnaire was administered at the visit.

4.5.1.2.2.1 MFM-32 Scoring

The MFM-32 contains 32 items to assess motor function, each measured on a scale of 0 to 3, for a total score of 96. The measures capture 3 dimensions of motor function:

- Standing and transfers (D1: 13 Items 6, 8, 11, 12, 24, 25, 26, 27, 28, 29, 30, 31 and 32)
- Axial and proximal motor function (D2: 12 Items 1, 2, 3, 5, 7, 9, 10, 13, 14, 15, 16 and 23)
- Distal motor function (D3: 7 Items 4, 17, 18, 19, 20, 21, and 22)

The score for each dimension corresponds to the sum of the scores obtained by the person for the items of this dimension divided by the maximum score for this dimension and multiplied by 100. For the unilateral items, the best score of the two sides at each visit will be used.

For the MFM-32, the total score is the sum of the 32 items scores divided by 96, as shown in the table below:

Table 2 MFM-32 Scoring

Measurement	Calculation
D1: Standing and Transfers	$D1\% = \frac{Sum\ of\ D1\ score}{13*3=39} * 100$
D2: Axial and Proximal	$D2\% = \frac{Sum\ of\ D2\ score}{12*3=36} * 100$
D3: Distal Motor Function	$D3\% = \frac{Sum\ of\ D3\ score}{7*3=21} * 100$
Total	$Total\% = \frac{Sum\ of\ total\ score}{32*3=96} * 100$

When all items are missing, the total score will be missing. When there are some missing item scores (but other items are available), the score for the missing item(s) will be imputed as 0.

4.5.1.2.2.2 MFM-20 Scoring

The MFM-20 was developed after the original MFM-32, and is a subset of the MFM-32 questionnaire. Items from the MFM-32 that are not considered validated for the <6 years old population are skipped for the administration of the MFM-20, though the numbering of the items remains the same.

The MFM-20 contains 20 items assessing motor function, each measured on a scale of 0 to 3, for a total score of 60. The measures capture 3 dimensions of motor function:

- Standing and transfers (D1: 8 Items 6, 11, 12, 24, 25, 27, 30, 32)

- Axial and proximal motor function (D2: 8 Items 1, 3, 5, 7, 9, 10, 14, 23)
- Distal motor function (D3: 4 Items 4, 18, 21, 22)

The score for each dimension corresponds to the sum of the scores obtained by the person for the items of this dimension divided by the maximum score for this dimension and multiplied by 100. For the unilateral items, the best score of the two sides at each visit will be used.For the MFM-20, the total score is the sum of the 20 items scores divided by 60, as shown in the table below:

Table 3 MFM-20 Scoring

Measurement	Calculation
D1: Standing and Transfers	$D1\% = \frac{Sum\ of\ D1\ score}{8*3=24} * 100$
D2: Axial and Proximal	$D2\% = \frac{Sum\ of\ D2\ score}{8*3=24} * 100$
D3: Distal Motor Function	$D3\% = \frac{Sum\ of\ D3\ score}{4*3=12} * 100$
Total	$Total\% = \frac{Sum\ of\ total\ score}{20*3=60} * 100$

The same missing data conventions described in Section 4.5.1.2.2.1 will be used for the MFM-20 scoring.

4.5.1.2.3 Change from baseline in total raw score in the gross motor domain of the Bayley Scales of Infant and Toddler Development III (Bayley-III) at Week 24

The raw Bayley-III gross motor domain scores and corresponding change from baseline at each visit will be summarized descriptively by dose level group.

The motor domain of the Bayley III is a standard series of measurements to assess the motor (fine and gross motor subscales) development of infants and toddlers.

To calculate the raw scores the following steps will be required:

1. For each task performed the child can receive either a credit point (1) or no credit (0)
2. Establish the Basal aka “floor”:
    2a. Identify the age of the child in months to determine the “start point” item

Age	Start Point	Item Number
16 days – 1 month 15 days	A	1
1 month 16 days – 2 months 15 days	B	1
2 months 16 days – 3 months 15 days	C	5
3 months 16 days – 4 months 15 days	D	9
4 months 16 days – 5 months 15 days	E	9
5 months 16 days – 6 months 15 days	F	15
6 months 16 days – 8 months 30 days	G	19
9 months 0 days – 10 months 30 days	H	22
11 months 0 days – 13 months 15 days	I	35
13 months 16 days – 16 months 15 days	J	39
16 months 16 days – 19 months 15 days	K	42
19 months 16 days – 22 months 15 days	L	45
22 months 16 days – 25 months 15 days	M	48
25 months 16 days – 28 months 15 days	N	48
28 months 16 days – 32 months 30 days	O	51
33 months 0 days – 38 months 30 days	P	54
39 months 0 days – 42 months 15 days	Q	57

2b. If the child has three consecutive scores of 1 beginning with their 'start point' item, then this is the Basal aka "floor".

2c. Otherwise, if any of the first 3 questions of the 'start point' are scored as 0, moving backwards towards 1, find the first instance prior to the initial start point where there are 3 consecutive questions with the score of 1. The first of these 3 will be the new "Basal".

2d. If there are no instances of 3 consecutive scores of 1 occurring before the initial 'start point', then the "Basal" will be item 1 regardless of how the child scored on questions 1, 2 and 3.

3. Establish the "Ceiling": the first time score of 0 appears on five consecutive items.
4. Count the number of items for which the child receives credit: "Basal" to "Ceiling". Anything after the "ceiling" value is considered as score 0 regardless of what's entered.
5. Count the number of items preceding the "Basal". Usually these will be un-administered, but there are instances where these questions have been administered despite the later 'start point'. Regardless of whether they are administered or un-administered, all the scores prior to the "Basal" should be counted as receiving credit (1).
6. Sum the numbers from step 4 and 5 to receive the raw score.

4.5.1.2.4 Change from baseline in total raw score in the fine motor domain of the Bayley-III at Week 24

The raw Bayley-III fine motor domain scores and corresponding change from baseline at each visit will be summarized descriptively by dose level group.

The motor domain of the Bayley III is a standard series of measurements to assess the motor (fine and gross motor subscales) development of infants and toddlers.

To calculate the raw scores the following steps will be required:

7. For each task performed the child can receive either a credit point (1) or no credit (0)
8. Establish the Basal aka "floor":

2a. Identify the age of the child in months to determine the "start point" item

Age	Start Point	Item Number
16 days – 1 month 15 days	A	1
1 month 16 days – 2 months 15 days	B	1
2 months 16 days – 3 months 15 days	C	1
3 months 16 days – 4 months 15 days	D	5
4 months 16 days – 5 months 15 days	E	10
5 months 16 days – 6 months 15 days	F	13
6 months 16 days – 8 months 30 days	G	15
9 months 0 days – 10 months 30 days	H	19
11 months 0 days – 13 months 15 days	I	22
13 months 16 days – 16 months 15 days	J	26
16 months 16 days – 19 months 15 days	K	28
19 months 16 days – 22 months 15 days	L	28
22 months 16 days – 25 months 15 days	M	31
25 months 16 days – 28 months 15 days	N	31
28 months 16 days – 32 months 30 days	O	35
33 months 0 days – 38 months 30 days	P	38
39 months 0 days – 42 months 15 days	Q	43

2b. If the child has three consecutive scores of 1 beginning with their 'start point' question, then this is the Basal aka "floor".

2c. Otherwise, if any of the first 3 questions of the 'start point' are scored as 0, moving backwards towards 1, find the first instance prior to the initial start point where there are 3 consecutive items with the score of 1. The first of these 3 will be the new "Basal".

2d. If there are no instances of 3 consecutive scores of 1 occurring before the initial 'start point', then the "Basal" will be item 1 regardless of how the child scored on questions 1, 2 and 3.

9. Establish the "Ceiling": the first time score of 0 appears on five consecutive items.
10. Count the number of items for which the child receives credit: "Basal" to "Ceiling". Anything after the "ceiling" value is considered as score 0 regardless of what's entered.
11. Count the number of items preceding the "Basal". Usually these will be un-administered, but there are instances where these questions have been administered despite the later 'start point'. Regardless of whether they are administered or un-administered, all the scores prior to the "Basal" should be counted as receiving credit (1).
12. Sum the numbers from step 4 and 5 to receive the raw score.

4.5.1.2.5 Change from baseline in the proportion of participants being able to feed without a gastrostomy or G-tube at Week 24

A participant's ability to feed without a gastrostomy tube (G-tube) is evaluated by the Parental Swallowing Questionnaire. A participant score of "Never (0)" on the first item of the

questionnaire, “Since the last visit how often do you use the following with your child – Tube Feeding” will indicate that the participant met the criteria in the endpoint at the visit.

A shift table of the number and proportion of participants meeting the criteria described above will be presented by dose level. The shift from baseline G-tube status to best post-baseline G-tube status will be summarized, as well as the shifts to each visit.

4.5.1.2.6 Change from baseline in the Communicative Development Inventories scores at Week 24

The Communicative Development Inventories scores and corresponding change from baseline at each visit will be summarized descriptively by dose level group.

CDI scores for each participant will be calculated as number of items marked by caregiver/ number of items on questionnaire. This is a raw, unadjusted score.

4.5.1.2.7 Change from baseline in the Parental Global Impression of Secretion Severity (PGIS-S) score at Week 24

The PGIS-S scores and corresponding change from baseline at each visit will be summarized descriptively by dose level group.

Parents/LAR/caregiver will report on the amount of suctioning and secretions management required over the previous week, using a scale of 1 to 7 (1 = not affected and 7 = among the worst he has ever been) to report impression of change from baseline and impression of current severity.

Missing values will not be imputed.

4.5.1.2.8 Change in the Parental Global Impression of Secretion Improvement (PGIS-I) score at Week 24

The PGIS-I scores at each visit will be summarized descriptively by dose level group.

Parents/LAR/caregiver will report on the amount of suctioning and secretions management required over the previous week, using a scale of 1 to 7 (1=very much improved and 7 = very much worse) to report impression of change from baseline.

Missing values will not be imputed.

4.5.1.2.9 Change from baseline in Clinical Global Impression of Severity (CGI-S) at Week 24

The CGI-S scores and corresponding change from baseline at each visit will be summarized descriptively by dose level group.

A global assessment by the Investigator or designee will be done to assess the severity of the participant’s disease utilizing a 7-point scale, where 1 = Normal, shows no signs of illness and 7 = among the most extremely ill of participants.

Missing values will not be imputed.

4.5.1.2.10 Change in the Clinical Global Impression of Improvement (CGI-I) score at Week 24

The CGI-I scores at each visit will be summarized descriptively by dose level group.

A global assessment by the Investigator or designee will be done to assess if there has been any improvement of the participant's disease utilizing a 7-point scale, where 1 = very much improved and 7 = very much worse.

Missing values will not be imputed.

4.6 Safety Analyses

The safety endpoints for this study are the following:

Adverse events (AEs), serious AEs (SAEs), and findings from safety laboratory tests, 12-lead electrocardiogram (ECG), echocardiograms (ECHOs), vital signs, growth parameters, physical examinations, liver ultrasounds, antibody formation (anti AAV8, anti MTM1), viral shedding, annualized hospitalization rate, annualized respiratory and non-respiratory SAE rate, and length of stay per hospitalization.

Safety analysis will be conducted for the SAF, unless specified otherwise.

4.6.1 Adverse Events

Treatment-emergent AEs (TEAEs) are defined as any AEs, regardless of relationship to study drug, that have an onset or worsening in severity on or after the time/date of the baseline (dosing) visit (the reference date).

All descriptive statistics will be presented by dose level and all dose levels combined. Unless otherwise indicated, AE summaries will be presented by the following periods:

- Baseline through Week 24 (inclusive)
- >Week 24 through Week 48
- >Week 48 to End of Study
- Overall for the study

An overview table to report the number and percentage of participants and number of events will include the following:

- TEAEs,
- Drug related TEAEs,
- Serious TEAEs,
- Serious drug related TEAEs,
- TEAEs leading to withdrawal of study
- Drug-related TEAEs leading to withdrawal of study
- TEAEs leading to death,
- Drug related TEAEs leading to death,
- NCI-CTCAE Grade 3 or higher TEAEs
- NCI-CTCAE Grade 3 or higher drug related TEAEs
- Deaths

NCI-CTCAE v4.03 or higher will be used for assessment of grade.

The number and percentage of participants with TEAEs, as classified by SOC and PT will be summarized for each treatment group and overall. Summaries will be provided for the following:

- TEAEs
- Drug related TEAEs,
- Serious TEAEs,
- Drug related serious TEAEs,
- TEAEs leading to withdrawal of study,
- Drug related TEAEs leading to withdrawal of study,
- NCI-CTCAE Grade 3 or higher TEAEs,
- NCI-CTCAE Grade 3 or higher drug-related TEAEs,
- TEAEs leading to death,
- Drug-related TEAEs leading to death,
- Frequently reported (>=10% in All Dosed Group) TEAEs by preferred term,
- Frequently reported (>=5% in Any Treatment Group) TEAEs Excluding Serious TEAEs (this table will only be presented for the overall study duration)

Related AEs are those with relationship to study medication reported as “possible” or “related”. If relationship to study drug of an AE reported by treated participants is not recorded, the relationship will be imputed as “possibly related”, for analysis purposes. In the participant listing, both collected and imputed values will be presented.

An overview table to report number of events, and events adjusted by participant year from date of drug exposure (each summary classified by category below, SOC and PT) will include the following:

- Serious respiratory TEAEs,
- Serious non-respiratory TEAEs

In the participant count, if a participant has multiple TEAEs with the same SOC or PT, but with differing severity, relationship, or action taken, then the participant will be counted once with the worst nonmissing severity grade, highest degree of relationship, or highest severity of action taken (Not Applicable < Dose Not Changed < Drug Interrupted < Drug Withdrawn). If severity, relationship, or action taken is missing for all episodes of the event, the participant will be counted under missing severity, relationship, or action taken. This summary will only be created for the ‘overall’ period.

The following adverse events of special interest (AESI) are defined by the following categories and corresponding MedDRA Version 26.0 SMQ search criteria. If MedDRA Version is upgraded, then the search criteria will be correspondingly upgraded to align with the updates:

- **Muscle abnormalities**
  - Rhabdomyolysis/myopathy (SMQ, broad and narrow)
  - Investigations (SOC)

        - Investigations, imaging and histopathology procedures (HLGT)
- **Myocarditis**
    - Noninfectious myocarditis/pericarditis (SMQ - broad)
- **Hepatobiliary disorders**
    - Hepatic Disorders (SMQ – broad)
        - Drug related hepatic disorders (SMQ - broad)
            - Cholestasis and jaundice of hepatic origin (SMQ - broad)
            - Drug related hepatic disorders - severe events only (SMQ - broad)
            - Liver related investigations, signs and symptoms (SMQ - broad)
            - Liver-related coagulation and bleeding disturbances (SMQ - broad)
    - Biliary disorders (SMQ - broad)
        - Functional, inflammatory and gallstone related biliary disorders (SMQ - broad)
            - Biliary system related investigations, signs and symptoms (SMQ - broad)
            - Biliary tract disorders (SMQ - broad)
            - Gallbladder related disorders (SMQ - broad)

The number and percentage of participants with AESIs, as classified by AESI category, SOC and PT will be summarized for each treatment group and overall. Summaries will be provided for the following:

- TEAEs
- Drug related TEAEs,
- Serious TEAEs,
- Drug related serious TEAEs,
- Grade 3 or higher TEAEs,
- Grade 3 or higher related TEAEs

Swimmer plots will be created, which will include information on glucocorticoid dosing (dose/duration) and AESI occurrence.

All AESIs will be listed.

All AEs that correspond to the MedDRA COVID-19 narrow SMQ search term will be listed separately.

4.6.2 Additional Safety Assessments

4.6.2.1 Clinical Laboratory Evaluation

The baseline value will be the last non-missing value taken prior to first dose of study drug.

Quantitative values evaluated by the central or local laboratory including hematology, serum chemistry, additional serum chemistry (includes complement panel, cytokine panel, and bile acids), coagulation, and urinalysis will be summarized using mean, standard deviation,

minimum, maximum and median by treatment group at each analysis visit. Additionally, a within-participant change will be calculated as the post-baseline measurement minus the baseline measurement and summarized in the same way. Each laboratory result will be classified as low (L), normal (N), or high (H) at each visit according to the laboratory supplied reference ranges.

Central lab results should be summarized if they're available at an analysis visit. If both local and central laboratory results are available at an analysis visit, the central lab values should be used preferentially for analysis. If only local labs are available at an analysis visit but central lab values are missing, then local labs may be used for analysis.

The number and percentage of participants below and above the reference range will be summarized for each dose level and overall at each visit.

Frequency tabulations of qualitative clinical laboratory variables (urinalysis) will be presented for each treatment group at each visit.

Selected laboratory abnormalities will be evaluated based on pre-specified threshold level (potentially clinically significant [PCS]) criteria. If both the baseline and on-treatment values of a parameter are beyond the same threshold limit for that parameter, then the on-treatment value will be considered a PCS value only if it is more extreme (farther from the limit) than was the baseline value. If the baseline value for a parameter is missing and the on-treatment value of a parameter is beyond the PCS limit, then the on-treatment value will be considered a PCS value. The pre-defined criteria for PCS laboratory values are presented below.

Table 4 Potentially Clinically Significant Laboratory Values

Pre-specified Threshold Values for Selected Laboratory Tests (Potentially Clinically Significant Laboratory Criteria)	
Laboratory Parameter	**Pre-Specified Level**
Chemistry	
Sodium	<132 mEq/L
Potassium	<3.0, <3.5, >5.0, >6.0 mEq/L
Serum bicarbonate	<10, <12, >30, >32 mEq/L
Creatinine	>25% increase from baseline
CK	>25% increase from baseline
ALT	>25% increase from baseline or 5 x ULN
AST	>25% increase from baseline or 5 x ULN
Glucose	>250 mg/dL
Troponin T and troponin I	>25% increase from baseline
Hematology	
Hemaglobin	<9 g/dL
Hematocrit	<27%

For each laboratory threshold criterion, the number and percent of participants who have a laboratory value meeting the threshold criteria during the investigational period will be summarized by dose level group and visit.

Laboratory results will be graded using NCI-CTCAE v4.03 or higher, where possible. NCI-CTCAE grade of laboratory evaluations will be summarized by number and percentage of participants at each visit.

The number and percentage of participants with ≥ Grade 1 shift from baseline in laboratory test result will be summarized by dose level and laboratory parameter.

The following data may be presented graphically by treatment group:

- Laboratory test results using box plot (by visits within each period),
- Change from baseline in laboratory test results using box plot (by visits within each period),
- Laboratory test results using spaghetti plot.

All laboratory results will be listed. Laboratory results that are above or below normal limits will be flagged, along with clinical significance, in the listings. In addition, laboratory results that meet or exceed the pre-specified levels (i.e., are above [or below as appropriate] the pre-specified levels as shown in the above table) will be flagged.

Should local laboratory values be collected, they will be listed and out of range values will be flagged.

4.6.2.2 Liver Safety Assessment

The liver safety assessments will be summarized by the categories below based on the measurements from Alkaline Phosphatase (ALP), Alanine Transaminase (ALT), Total Bilirubin, Aspartate Transaminase (AST) and their combination. These parameters will be based on measurements from all laboratory (central and local [when units/reference ranges are available]).

The participant's highest value during any post-dose follow-up visit in the following periods will be summarized by period:

- Baseline through Week 24 visit (inclusive)
- >Week 24 through Week 48 visit
- >Week 48 to End of Study visit
- Overall for the study

Table 5 Liver Function Test Thresholds

Liver Test	Criteria
ALT	>3 x ULN
	>5 x ULN
	>10 x ULN
	>20 x ULN
AST	>3 x ULN
	>5 x ULN
	>10 x ULN
	>20 x ULN
Total Bilirubin	>2 x ULN
Direct Bilirubin	>2 x ULN
Serum Bile Acids	>2 x ULN

Liver Test	Criteria
ALP	>1.5 x ULN
ALT and/or AST and Total Bilirubin	(ALT and/or AST> 3 x ULN) and (Total Bilirubin > 2 x ULN)
ALT and Total Bilirubin	(ALT > 3 x ULN) and (Total Bilirubin > 2 x ULN)
ALT and Direct Bilirubin	(ALT > 3 x ULN) and (Direct Bilirubin > 2 x ULN)
ALT and/or AST, Total Bilirubin, and ALP	(ALT and/or AST> 3 x ULN) and (Total Bilirubin > 2 x ULN) and (ALP < 2 x ULN)

Criteria where 2 or more parameters are evaluated will be with the measurements on the same day or up to 1 day apart. The denominator for each criterion will be the number of participants who have at least one value during the 24 week investigational period. The number and percentage of participants meeting the criteria during the 24 week investigational period will be summarized by treatment group. In addition, a by-visit summary showing the number of participants achieving these thresholds will be provided.

Change from baseline in special liver laboratory parameters of interest (eg, bilirubin, AST, ALT, and CK) will be summarized descriptively.

The following data may be presented graphically by treatment group:

- Matrix scatter plot of maximum liver tests values during each period of the study,
- eDISH plot
- Individual display of liver tests for selected participants experiencing potentially clinically significant criteria in liver tests.
- Individual line plots display of selected liver tests in terms of xULN will be provided as described in Section 4.2.6.

4.6.2.3 Vital Signs

The baseline value will be the last non-missing value taken prior to first dose of study drug.

Vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], temperature, and heart rate) will be summarized using mean, standard deviation, minimum, maximum and median by treatment group and visit. Additionally, a within-participant change will be calculated per visit as the post-baseline measurement minus the baseline measurement and summarized by treatment group and overall at each visit.

A separate table will be provided to summarize respiration rate for participants off ventilator using mean, standard deviation, minimum, maximum and median by treatment group, age group, and visit.

Tables for potentially clinically significant vital signs will be generated using baseline value and highest/ lowest value obtained during treatment for each participant for each treatment group.

The following potentially clinically significant criteria are defined for each parameter:

Table 6 Potentially Clinically Significant Criteria for Vital Signs

Vital Sign Variable	Age Group	Criteria (Low)	Criteria (High)
SBP	1 – 12 Months	< 72 mmHg	>104
	1 – 2 Years	< 86 mmHg	>106 mmHg
	3 – 5 Years	< 89 mmHg	>112 mmHg
	6 – 7 Years	< 97 mmHg	>115 mmHg
	≥ 8 Years	< 102 mmHg	>131 mmHg
DBP	1 – 12 Months	< 37	>56
	1 – 2 Years	< 42 mmHg	>63 mmHg
	3 – 5 Years	< 46 mmHg	>72 mmHg
	6 – 7 Years	< 57 mmHg	>76 mmHg
	≥ 8 Years	< 64 mmHg	>83 mmHg
HR	1 – 12 Months	< 111 bpm	>182 bpm
	1 – 2 Years	< 108 bpm	>180 bpm
	3 – 5 Years	< 88 bpm	>152 bpm
	6 – 7 Years	< 75 bpm	>118 bpm
	≥ 8 Years	< 60 bpm	>100 bpm
RR	1 – 12 Months	< 27 bpm	>45 bpm
	1 – 2 Years	< 21 bpm	>43 bpm
	3 – 5 Years	< 18 bpm	>31 bpm
	6 – 7 Years	< 17 bpm	>25 bpm
	≥ 8 Years	< 12 bpm	>22 bpm

BL = baseline, SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, RR = respiratory rate

All vital signs parameters will be listed. The listing will flag any vital signs that exceed the levels provided in the table above.

4.6.2.4 Electrocardiograms

ECG variables will be summarized using mean, standard deviation, minimum, maximum and median for each treatment group and overall at each treatment visit and time point, including changes from baseline.

Number and percent of participants with normal, not clinically significant abnormal, and clinically significant abnormal results as assessed by investigator for the 12 lead ECG will be tabulated by treatment group and overall at each treatment visit and time point.

The heart rate, PR, and QTc interval will be summarized using frequency tables for each treatment visit and time point for values of clinical importance using the range criteria below.

Table 7 Potentially Clnically Significant Criteria for ECG

ECG Parameter	Age Group	Pre-specified Level
PR	6 – 11 months	<70, >159
	12 – 23 months	<71 msec, >160 msec
	2 – 3 years	<75 msec, >165 msec
	4 – 5 years	<80 msec, >166 msec
	6 – 7 years	<83 msec, >170 msec
	> 7 years	<85 msec, >182 msec
QTc (Fridericia's)	Any	>450 msec, > 480 msec, >500 msec
QRS	6 – 11 months	< 40, > 101 milliseconds
	12 – 23 months	< 40, > 105 msec
	2 – 3 years	< 40, > 115 msec
	4 – 5 years	< 41, > 125 msec
	6 – 7 years	< 52, > 118 msec
	> 7 years	< 60, > 122 msec
Heart rate	6 – 11 months	< 65, 188 beats/min
	12 – 23 months	< 56, > 184 beats/min
	2 – 3 years	< 46, > 168 beats/min
	4 – 5 years	< 38, > 146 beats/min
	6 – 7 years	< 40, > 128 beats/min
	> 7 years	< 30, > 122 beats/min

The QTc interval will also be summarized by the frequencies of participants with a change from baseline of clinical importance using the criteria identified below. These summaries will be provided for each treatment visit and time point.

Table 8 Potentially Clnically Significant Criteria for QTc

Variable	Change from Baseline
QTc Interval (msec)	> 30 > 60

Number and percent of participants whose 12 lead ECG reading changed from normal at baseline to abnormal will be tabulated by treatment group at each treatment visit and time point.

Listings will present ECG data, such as overall interpretation of ECGs, assessments of heart rate (HR), and intervals of PR, QRS, QT, QTc (with method), as well as other specifications. The listing will flag any results that are outside the levels provided in the table above.

4.6.2.5 Other Safety-Related Assessments

4.6.2.5.1 Echocardiogram

Number and percentage of participants with abnormal ECHO findings will be summarized by time point (and clinical significance if feasible). Participant listings of ECHO findings and descriptions will be provided.

4.6.2.5.2 Liver Ultrasound

Number and percentage of participants with abnormal liver ultrasound findings will be summarized by time point and clinical significance if feasible. Participant listing of liver ultrasound findings and descriptions will be provided.

4.6.2.5.3 Hospitalization

The annualized hospitalization rate will be summarized by dose level group and overall. The participant-year-adjusted rate is calculated for each participant by:

$$\frac{Sum\ of\ the\ number\ of\ hospital\ admissions\ recorded\ on\ the\ AE\ eCRF}{(max(Date\ of\ last\ day\ of\ follow\ up, date\ of\ discontinuation) - date\ of\ dosing + 1)/\ 365.25}$$

Summary statistics of this rate will be tabulated. In addition, the annualized hospitalization rate will be summarized by counts and percentages in the following categories:

- 0 hospitalizations
- < 1 hospitalization/patient-year
- 1-2 hospitalization/patient-year
- 2-3 hospitalizations/patient-year
- 3-4 hospitalizations/patient-year
- 4-5 hospitalizations/patient-year
- >= 5 hospitalizations/patient-year

Length of stay per hospitalization will be summarized descriptively as a continuous variable. Length of stay is calculated as the discharge date – admission date + 1. If a participant has multiple hospital stays with multiple corresponding durations, then all will be included in the summary statistics.

Participants' hospitalization information will also be listed.

4.6.2.6 Growth Parameters and Physical Examination

Growth parameters will be summarized descriptively.

Growth parameters and physical examinations will be listed.

4.7 Other Analyses

4.7.1 Other Variable and/or Parameters

4.7.1.1 Analysis of Immunogenicity

All available antibody titer (anti-AAV8 (NAB), anti-AAV8 (TAB), anti-MTM1) data will be included in a participant listing. Antibody titers that are below the limit of detection (BLD) values will be presented as "BLD" in the listing and footnoted accordingly.

Summaries will be created for tabulating the incidence (and percent) of immune response by treatment group and assay type.

Spider plots of titer levels will be created by dose level group for each assay type.

4.7.1.2 Biodistribution and Vector Shedding

All available vector DNA in muscle biopsy data and vector shedding data will be included in a participant listing.

Vector DNA in muscle bioposies will be summarized descriptively by visit and dose level group.

Maximum vector DNA concentrations (Cmax) and time to achieve maximum concentration in shedding matrices (Tmax) will be summarized descriptively by dose level group.

The duration of vector shedding will be summarized descriptively by dose level using Kaplan-Meier plots along with median (95% CI) and quartile time from the administration of study drug to event. Additional summary statistics will be provided for participants who are not censored.

The event of 'end of vector shedding' is defined as the date of the first of three vector shedding results measured as below the lower limit of quantification (LLOQ). Participants will be censored at the last known date/time of contact.

Spider plots of vector shedding data over time will be created by dose level group.

4.7.2 Subgroup Analyses

Subgroup analyses are not planned for this study.

4.8 Interim Analysis (and Early Discontinuation of the Clinical Study)

There will be no formal interim analysis.

4.9 Sample Size Determination

The following language was from protocol v9 that planned a formal analysis to compare 1.3×10^{14} vg/kg and delayed-treatment control, however given that the study will not be able to address the objectives, no such formal analysis will be conducted.

A power analysis for the primary analysis of the primary endpoint was conducted at 80% power and 0.05 level of alpha to estimate the required sample size based on Mean of 13.0 vs. 0.0 hours of reduction in ventilation need, with common SD of 6.0 by Week 24 using a t-test, resulting in at least N = 10 for a balanced 1:1 allocation between 1.0×10^{14} vg/kg AT132 (equates to 1.3×10^{14} vg/kg as determined by the 2nd generation vg titer assay) and delayed-treatment control. It is further assumed, that the same difference in means (SD), will provide at least 80% power using a MMRM analysis proposed for the primary endpoint. However, it is possible that 1:1 allocation may not be feasible; 1 control participant serving as control for multiple treated participants, or multiple control participants being a match for a single treated participant. Therefore, all qualified control participants will be used in the analyses to

ensure adequate power is available to detect the intended difference between treated and control participants.

4.10 Additional Conventions

4.10.1 Baseline Definition

Unless otherwise specified, baseline is defined as the last assessment collected in ASPIRO study prior to time/date of dosing with study drug.

4.10.2 Analysis Windows

The data summary by visits will be done following the analysis windows specified in the tables below:

Table 9 Analysis Visit Windows for Efficacy Endpoints

Analysis Visits	Scheduled Day in Protocol (Day)	Analysis Windows (Day)								
		(a) Ventilator param., MIP, MEP, P0.1, tidal volume, ventilator weaning & discont.	(b) Secretion manage. assessment (PGIS-S, PGIS-I)	(c) Motor develop. milestone,	(d) Bayley-III, motor domain	(e) CHOP INTEND, MFM-32	(f) ACEND	(g) PedsQL	(h) Clinical global impression scales, Swallowing questionnaire, Communicative development inventories	(i) Ventilator Depend. Question.
Baseline	-1	≤ -1	≤ -1	≤ -1	≤ -1	≤ -1	≤ -1	≤ -1	≤ -1	≤ -1
Dosing	1									
Day 2	2									
Day 3	3									
Week 1	7						1-10	1-10	1-10	1-17
Week 2	14	1-21				1-21	11-21	11-21	11-21	
Week 3	21									
Week 4	28	22-56	1-42	1-56	1-56	22-42	22-56	22-56	22-42	18-56
Week 5	35									
Week 6	42									
Week 7	49									
Week 8	56		43-70			43-70			43-70	
Week 9	63									
Week 10	70									
Week 11	77									
Week 12	84	57-98	71-98	57-98	57-98	71-98	57-98	57-98	71-98	57-98
Week 13	91									
Week 14	98									
Week 15	105									
Week 16	112	99-140	99-126	99-140	99-140	99-140	99-140	99-140	99-140	99-140
Week 20	140		127-154							
Week 24	168	141-252	155-182	141-210	141-210	141-210	141-210	141-210	141-210	141-182
Week 28	196		183-210							183-210
Week 32	224		211-238							211-238
Week 36	252		239-266	211-294	211-294	211-294	211-294	211-294	211-294	239-266
Week 40	280		267-294							267-294
Week 44	308		295-322							295-322
Week 48	336	253-442	323-442	295-396	295-396	295-442	295-442	295-442	295-442	323-396
Month 15	456			397-502	397-502					397-502
Month 18	548	443-639	443-639	503-639	503-639	443-639	443-639	443-639	443-639	503-639

Analysis Visits	Scheduled Day in Protocol (Day)	Analysis Windows (Day)								
		(a) Ventilator param., MIP, MEP, P0.1, tidal volume, ventilator weaning & discont.	(b) Secretion manage. assessment (PGIS-S, PGIS-I)	(c) Motor develop. milestone,	(d) Bayley-III, motor domain	(e) CHOP INTEND, MFM-32	(f) ACEND	(g) PedsQL	(h) Clinical global impression scales, Swallowing questionnaire, Communicative development inventories	(i) Ventilator Depend. Question.
Month 24	730	640-821	640-821	640-821	640-821	640-821	640-821	640-821	640-821	640-821
Month 30	913	822-1004	822-1004	822-1004	822-1004	822-1004	822-1004	822-1004	822-1004	822-1004
Month 36	1095	1005-1186	1005-1186	1005-1186	1005-1186	1005-1186	1005-1186	1005-1186	1005-1186	1005-1186
Month 42	1278	1187-1369	1187-1369	1187-1369	1187-1369	1187-1369	1187-1369	1187-1369	1187-1369	1187-1369
Month 48	1460	1370-1551	1370-1551	1370-1551	1370-1551	1370-1551	1370-1551	1370-1551	1370-1551	1370-1551
Month 54	1643	1552-1734	1552-1734	1552-1734	1552-1734	1552-1734	1552-1734	1552-1734	1552-1734	1552-1734
Month 60	1825	≥1735	≥1735	1735-2007	≥1735	≥1735	1735-2007	≥1735	≥1735	1735-2007
Month 72	2190			2008-2372			2008-2372			2008-2372
Month 84	2555			2373-2737			2373-2737			2373-2737
Month 96	2920			2738-3102			2738-3102			2738-3102
Month 108	3285			3103-3467			3103-3467			3103-3467
Month 120	3650			≥3468			≥3468			≥3468

Abbreviations: NA = Not Applicable.
Grey area indicates NA.

Table 10 Analysis Visit Windows for Safety Endpoints

Analysis Visits	Scheduled Day in Protocol (Day)	Analysis Windows (Day)												
		(a) LFTs, CK (including CK isoenzymes), CRP, serum bicarbonate (local &central)	(b) Chemistry excluding (a), hematology (local & central)	(c) Urinalysis (local & central)	(d) Cytokine panel, complement panel (central)	(e) Troponin T and/or I (local & central)	(f) Coagulation (local)	(g) Viral Shedding (central)	(h) Serum bile acid (central)	(i) Platelet monitoring	(i) Vital signs	(j) 12-Lead ECG	(k) Liver ultrasound	(l) Anti-AAV8, Anti-MTM1 (central)
Baseline	-1	≤ -1	≤ -1	≤ -1	≤ -1[#]	≤ -1	≤ -1		≤ -1	≤ -1	≤ 1*	≤ -1	≤ -1	
Dosing	1							1			1*			
Day 2	2	1-4	1-4	1-4		1-4		2		1-4	2	1-4		
Day 3	3				1-5			3-5			3-5			
Wk 1	7	5-10	5-10	5-10	6-10	5-10	1-17	6-14		5-10	6-10	5-10		
Wk 2	14	11-17	11-21	11-21	11-17	11-17				≥11	11-21	11-21		
Wk 3	21	18-24			18-24	18-24		15-28						
Wk 4	28	25-31	22-42	22-42	25-31	25-35	18-42				22-42	22-42	1-56	1-35
Wk 5	35	32-38			32-38			29-42						
Wk 6	42	39-45			39-45	36-49								36-49
Wk 7	49	46-52			46-52			43-56						
Wk 8	56	53-59	43-70	43-59	53-59	50-59	43-112				43-70	43-70		50-70
Wk 9	63	60-66		60-66	60-66	60-66		57-70						
Wk 10	70	67-73		67-73	67-73	67-73								
Wk 11	77	74-80		74-80	74-80	74-80		71-84						
Wk 12	84	81-87	71-98	81-98	81-87	81-87			1-126		71-98	71-98	57-98	71-98
Wk 13	91	88-94			88-94	88-94		85-98						
Wk 14	98	95-101			95-101	95-101								
Wk 15	105	102-108			102-108	102-108		99-136						
Wk 16	112	109-140	99-140	99-140	109-140	109-140					99-140	99-140	99-140	99-140
Wk 24	168	141-210	141-210	141-210	141-210	141-210	113-210	137-210	127-210		141-210	141-210	141-210	141-210
Wk 36	252	211-294	211-294	211-294	211-294	211-294	211-294	211-294	211-294		211-294	211-294	211-294	211-294
Wk 48	336	295-442	295-442	295-442	295-442	295-442	295-442	295-442	295-396		295-396	295-442	295-442	295-442
Mth 15	456								397-502		397-502			
Mth 18	548	443-639	443-639	443-639	443-639	443-639	443-639	443-639	503-639		503-639	443-639	443-639	443-639
Mth 24	730	640-821	640-821	640-821	640-821	640-821	640-821	640-821	640-821		640-821	640-821	640-821	640-821
Mth 30	913	822-1004	822-1004	822-1004	822-1004	822-1004	822-1004	822-1004	822-1004		822-1004	822-1004	822-1004	822-1004
Mth 36	1095	1005-1186	1005-1186	1005-1186	1005-1186	1005-1186	1005-1186	1005-1186	1005-1186		1005-1186	1005-1186	1005-1186	1005-1186

Footnotes

Analysis Visits	Scheduled Day in Protocol (Day)	Analysis Windows (Day)												
		(a) LFTs, CK (including CK isoenzymes), CRP, serum bicarbonate (local &central)	(b) Chemistry excluding (a), hematology (local & central)	(c) Urinalysis (local & central)	(d) Cytokine panel, complement panel (central)	(e) Troponin T and/or I (local & central)	(f) Coagulation (local)	(g) Viral Shedding (central)	(h) Serum bile acid (central)	(i) Platelet monitoring	(i) Vital signs	(j) 12-Lead ECG	(k) Liver ultrasound	(l) Anti-AAV8, Anti-MTM1 (central)
Mth 42	1278	1187-1369	1187-1369	1187-1369	1187-1369	1187-1369	1187-1369	1187-1369	1187-1369		1187-1369	1187-1369	1187-1369	1187-1369
Mth 48	1460	1370-1551	1370-1551	1370-1551	1370-1551	1370-1551	1370-1551	1370-1551	1370-1551		1370-1551	1370-1551	1370-1551	1370-1551
Mth 54	1643	1552-1734	1552-1734	1552-1734	1552-1734	1552-1734	1552-1734	1552-1734	1552-1734		1552-1734	1552-1734	1552-1734	1552-1734
Mth 60	1825	≥1735	1735-2007	≥1735	≥1735	≥1735	≥1735	≥1735	≥1735 1735-2007@		≥1735	≥1735	1735-2007	≥1735
Mth 72	2190		2008-2372						2008-2372@				2008-2372	
Mth 84	2555		2373-2737						2373-2737@				2373-2737	
Mth 96	2920		2738-3102						2738-3102@				2738-3102	
Mth 108	3285		3103-3467						3103-3467@				3103-3467	
Mth 120	3650		≥346						≥3468@				≥3468	

Abbreviations: CRP = C-creative protein; Local = Local Lab; Central = Central Lab; NA = Not Applicable; Wk = Week; Mth = Month.

Grey area indicates NA.

#Only Applicable to Cytokine panel.

*As per the study protocol and SAP: For Vital Signs assessment on Dosing Day 1, if the assessment time was prior to Dosing time, then the assessment will be used as Baseline; if the assessment time is after Dosing time, then the assessment will be under "Day 1" visit.

@Only Applicable to Serum Bile Acid, Total.

Table 11 Analysis Week Window for Weekly Average Hours of Ventilator Support from Diary of Ventilator Dependence

Analysis Week	Analysis Windows (Day)
Baseline	-7 - -1
Week 1	1 – 7
Week 2	8 – 14
Week 3	15 - 21
Week 4	22 – 28
Week 5	29 – 35
Week 6	36 – 42
Week 7	43 – 49
Week 8	50 – 56
Week 9	57 – 63
Week 10	64 – 70
Week 11	71 – 77
Week 12	78 – 84
Week 13	85 – 91
Week 14	92 – 98
Week 15	99 – 105
Week 16	106 – 112
Week 17	113 – 119
Week 18	120 – 126
Week 19	127 – 133
Week 20	134 – 140
Week 21	141 – 147
Week 22	148 – 154
Week 23	155 – 161
Week 24	162 – 168
Week 25	169 – 175
Week 26	176 – 182
Week 27	183 – 189
Week 28	190 – 196
Week 29	197 – 203
Week 30	204 - 210
Week 31	211 – 217
Week 32	218 – 224
Week 33	225 – 231
Week 34	232 – 238
Week 35	239 - 245
Week 36	246 – 252
Week 37	253 – 259
Week 38	260 – 266
Week 39	267 – 273
Week 40	274 - 280
Week 41	281 – 287
Week 42	288 – 294
Week 43	295 - 301
Week 44	302 - 308
Week 45	309 – 315
Week 46	316 – 322
Week 47	323 – 329
Week 48	330 – 336

If more than one observation exists within the analysis window, the observation closest to the scheduled visit day will be selected for that visit. If there are two observations that have the same distance from the scheduled day, the value that is after the scheduled day will be

selected in the analysis. If more than one observation is made on the same day, an average value if continuous or the worst value if categorical will be included in the analysis.

The Follow Up visit will include all data collected beyond 10 days after the last dose of study drug. If there is more than one value, then the value that is closest to day 28 from the last dose of study drug will be selected for the analysis. The same logic will be applied as above for more than one value.

If a table summary for visits is not planned, then visit windowing does not need to be done for that data.

For diary data, results will be mapped to a particular visit week by the following logic, which is the same as in Table 11:

avisit="Week "||strip(put(ceil(ady/7),best.))

Per protocol, daily diary collection should end after Week 48. However, for some participants it continued longer. For daily diary analysis visits that correspond to a “Month X” official analysis visit name, the avisit calculation above will be converted to the corresponding Month X official analysis according to the analysis windows table.

4.10.3 Imputation Rules for Incomplete Dates

In case of missing or partial start and stop dates for concomitant medications, the following rules will be used:

If the start date is missing or partial:

- if the month is missing, use January
- if the day is missing, use the first day of the month under consideration
- if the year is missing, use year of the informed consent date
- if the entire date is missing, use informed consent date

If the stop date is missing or partial:

- if the month is missing, use December
- if the day is missing, use the last day of the month under consideration
- if the year or the entire date is missing, set the stop date to December 31st, 2099

If the imputed start date is after the stop date, then the imputed start date will be 1 day prior to the stop date.

For AEs, a missing or incomplete onset date will be imputed according to the following conventions.

If an onset date is missing or only the year is known, the imputed onset date will be the date of first dose of study drug.

If only the year is known for the AE onset date, the imputed onset date will be the latest of the following non-missing dates:

- Date of first dose of study drug

- January 1 of the year of AE onset date

If only the month and year is known for the onset date, set the surrogate onset date to the first day of that month and then apply the following rules.

- If the month and year of the onset date is prior to the month and year of the first dose of study drug, then the surrogate onset date will be the imputed onset date.
- If the month and year of the onset date is on or after the month and year of the first dose of study drug, then the imputed onset date will be the **latest** of the following non-missing dates:
  - Date of first dose of study drug
  - Surrogate onset date
    - If the imputed onset date is after the adverse event end date, the imputed onset date will be the same as the adverse event end date.

5 SUPPORTING DOCUMENTATION

5.1 Appendix 1 List of Abbreviations

Abbreviations	Description of abbreviations
ACEND	Assessment of Caregiver Experience with Neuromuscular Disease
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine transaminase
AST	aspartate transaminase
Bayley-III	Bayley Scales of Infant and Toddler Development III
BLD	below the limit of detection
CDI	Communicative Development Inventories
CGI-I	Clinical Global Impression of Improvement
CGI-S	Clinical Global Impression of Severity
CHOP INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CI	confidence interval
CS	compound symmetry
DBP	diastolic blood pressure
DMC	data monitoring community
DMI	Developmental Milestone Identifiers
ECG	ectrocardiogram
ECHO	echocardiogram
FAS	full analysis set
GM	gross motor (Bayley)
GMFR	geometric mean fold rise
GMT	geomtric mean titer
ICH	International Conference on Harmonization
LAR	legally authorized representative
LLOQ	lower limit of quantification
LOCF	last observation carried forward
LS	least squares
MFM	Motor Function Measure scale
MIP	maximal inspiratory pressure
MMRM	mixed model repeated measures
n	participants
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PCS	potentially clinically significant
PedsQL	Pediatric Quality of Life Inventory
PGIS-I	Parental Global Impression of Secretion Improvement
PGIS-S	Parental Global Impression of Secretion Severity
PT	preferred term
SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
SMA-I	spinal muscular atrophy type I
SOC	system organ class
ULN	upper limit of normal
UN	unstructured
WHO	World Health Organization
XLMTM	X-Linked Myotubular Myopathy

5.2 Appendix 2 Unfavorable Values for Efficacy Estimand Imputation

Endpoint	Variable	Imputed value after ICE occurrence through Week 48
Primary	Hours of ventilation support	24 hours
Key Secondary	Achieving functionally independent sitting for at least 30 seconds	No (0)
Secondary	CHOP INTEND Total Score	0
	MIP	0
	Myotubularin expression	0
	ACEND total score	0
	PedsQL Scale	0
	PedsQL Summary Score	0
	Number of age-appropriate gross motor function milestones achieved	0
	Full ventilator independence achieved	No

ICE = intercurrent event

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7 SIGNATURE

(E-signatures are attached at the end of document)

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